CHAPTER 6

Non–small-cell lung cancer

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Lung cancer has been the leading cause of cancer death among men in the United States for years, and since 1988, it has become the number-one cause of cancer death among women. An estimated 172,570 new cases of lung cancer are expected in 2005, and 163,510 deaths due to this disease are expected to occur. This exceeds the combined number of deaths from the leading causes of cancer (breast, prostate, and colon cancer). It accounts for 6% of all deaths in the United States.

Lung cancer develops from pulmonary parenchymal or bronchial supportive tissues. Although multiple cell types are often found within a single lung tumor, one type usually predominates. Based on therapeutic approach, there are two major subdivisions of lung cancer: small-cell lung cancer (SCLC), for which chemotherapy is the primary treatment, and non–small-cell lung cancer (NSCLC), which in its early stages (I and II) is treated primarily with surgery. Nearly all cures in NSCLC involve surgery.

This chapter provides basic information on the epidemiology, etiology, screening, prevention, and signs and symptoms of lung cancer in general, and then focuses specifically on the diagnosis, staging, pathology, and treatment of NSCLC and carcinoid tumors of the lungs, as well as the pulmonary evaluation of lung cancer patients and follow-up of long-term survivors.

Chapter 7 provides information on the staging, pathology and pathophysiology, and treatment of the far less common SCLC and concludes with brief discussions of mesothelioma and thymoma.

Epidemiology

Gender From 1995 to 1999, there were 86 cases of lung cancer per 100,000 men and 57 cases of lung cancer per 100,000 women. Although the incidence of lung cancer had been rising in women, the rate of increase has begun to slow recently.

Age The age at which lung cancer patients are diagnosed varies widely, but the median age at diagnosis is approximately 70 years.

Race In the United States, the highest incidence of lung cancer is found in Hawaiians and African-Americans.

Geography There are geographic variations in the incidence of lung cancer, with the highest rates worldwide observed in Scotland and Wales and the highest rates in the United States found in northern urban areas and along the southern coast from Texas to Florida.

Survival The overall 5-year survival rate for lung cancer is 12%.

Etiology and risk factors

Cigarette smoking Approximately 87% of all cases of lung cancer are related to cigarette smoking. There is a relatively strong dose-response relationship between cigarette smoking and the development of this cancer. The greater the number of cigarettes smoked on a daily basis and the greater the number of years of smoking, the greater is the risk of lung cancer. An individual who smokes one pack of cigarettes daily has a 20-fold increased risk of lung cancer compared to a nonsmoker.

The overall incidence of cigarette smoking decreased from 1974 through 1992. Smoking cessation decreases the risk of lung cancer, but a significant decrease in risk does not occur until approximately 5 years after stopping, and the risk remains higher in former smokers than in nonsmokers for at least 25 years. The benefit of smoking cessation is greater if it occurs at a younger age.

Smoking cessation is difficult. Recent data have suggested that a variety of hereditary factors increase the risk of addiction to nicotine among some individuals. Nevertheless, millions of former smokers have quit successfully. Smoking cessation programs that address both physical withdrawal from nicotine and psychological dependence appear to be more effective than either of these approaches alone. In addition, continued efforts are needed to prevent adolescents and preadolescents from beginning to smoke or to encourage them to quit after a brief period of experimentation.

Several cancer centers have recently reported that more than half of their patients with newly diagnosed lung cancer are former smokers, having quit more than 1 year before diagnosis. Healthy ex-smokers represent a large group of individuals who may benefit from effective tools for early detection and/or chemoprevention of lung cancer.

Secondhand smoke Not only is smoking risky for those who smoke, but it also poses a hazard to nonsmokers who either live or work with smokers. It is estimated that approximately 3,000 lung cancer deaths per year in the United States are due to secondhand smoke. Individuals who live in a household with a smoker have a 30% increase in the incidence of lung cancer compared to nonsmokers who do not live in such an environment.

Asbestos exposure is another risk factor for lung cancer. Cigarette smokers who are exposed to asbestos develop lung cancer at an extremely high rate. Exposure to asbestos is also a major risk factor for the development of mesothelioma (see discussion of this cancer in the following chapter).

Radioactive dust and radon exposure Uranium miners who have been exposed to radioactive dust and radon gas also have an increased incidence of lung cancer. Although there has been some controversy about the risk posed by exposure to residential radon gas, a recent study conducted in Sweden showed an increased incidence of lung cancer in individuals who were exposed to a high level of radon in their homes.

Screening and prevention

Screening

Currently, screening for lung cancer among asymptomatic individuals at elevated risk due to smoking history or occupational exposures is not recommended, and the US strategy for diagnosis and treatment of lung cancer is to do nothing until the patient presents with symptoms. An unfortunate result of this policy is that most patients present in advanced stage, and cure rates have improved little over the past 30 years. Only 7% of NSCLC patients are diagnosed in stage IA.

Three randomized screening trials conducted in the United States in the 1970s failed to show a reduction in lung cancer mortality among the smokers who were screened by sputum cytology and chest x-ray for lung cancer. Despite the fact that these American trials were not designed to evaluate chest x-ray as a screening tool, the results led most experts to conclude that screening for lung cancer was not worthwhile. In addition, most investigators recommended that research efforts and resources be allocated to the *prevention* of lung cancer. A more recent, randomized, prospective trial from Czechoslovakia showed that screening with a chest x-ray increased the diagnosis of early-stage lung cancer but failed to reduce the mortality from lung cancer.

The potential to screen for lung cancer has received renewed interest due to the superior performance of low-dose helical CT compared with chest radiography in detecting small lesions. Although there is insufficient evidence to establish policy related to routine screening for lung cancer with spiral CT, there is a growing trend toward promoting screening with this new technology to individuals at increased risk for lung cancer.

Numerous studies are currently under way to evaluate chest CT scan for lung cancer screening. Several recent reports from Japan, Germany, and the United States have documented the ability of low-dose spiral CT scans to detect lung cancer at an early stage. In some recent trials, more than 80% of lung cancers detected by screening were diagnosed in stage I.

Kaneko screened male smokers > 50 years of age. Of the 15 cancers detected by CT scan, only 4 were seen on chest x-ray; 14 of the 15 cancers were stage I, with an average diameter of 1.6 cm. Ohmatsu found 35 lung cancers (0.37% detection rate) with 9,452 CT scans. Of these cancers, 27 were stage IA. These patients had a 3-year survival rate of 83%.

The International Early Lung Cancer Action Project (I-ELCAP, http://www.ielcap.org/professionals.htm) is a single-arm prospective study that has accrued more than 26,000 study subjects and documented that a high percentage of lung cancers are detected in stage I, a stage in which long-term survival can reasonably be anticipated in more than 60% of patients. These studies provide early evidence to suggest that CT lung cancer population screening has the potential to reduce lung cancer mortality in the near future.

Henschke et al recently reported encouraging results from ELCAP of screening with spiral CT scan. Included in the initial report were 1,000 symptom-free volunteers, aged 60 years or older, with at least 10 pack-years of cigarette smoking and no previous cancer who were medically fit to undergo thoracic surgery. Noncalcified pulmonary nodules were detected in 233 participants (23% [95% CI: 21-26]) by low-dose CT at baseline, compared with 68 (7% [95% CI: 5-9]) by chest radiography. Lung cancer was detected by CT in 27 patients (2.7% [95% CI: 1.8-3.8]) and by chest radiography in 7 patients (0.7% [95% CI: 0.3-1.3]).

Of the 27 CT-detected cancers, 26 were resectable. Stage I cancers were diagnosed in 23 of 27 patients (85%) by CT and 4 of 7 patients (57%) by chest radiography. In addition, low-dose CT detected four more nonparenchymal cases of lung cancer: two with endobronchial lesions and two in the mediastinum. These cases show an added benefit of low-dose CT over chest radiography, although the data were not included in the analysis. (The study primarily focused on malignant disease in noncalcified pulmonary nodules detected by low-dose CT or radiography.) It remains to be seen, however, whether lung cancer screening with low-dose spiral CT will reduce the lung cancer mortality of the study population or only improve the 5-year survival rate of the patients diagnosed with lung cancer.

Based on growing evidence that spiral CT may truly provide for a successful early detection strategy, the National Cancer Institute (NCI) launched the National Lung Screening Trial (NLST, http://www.nci.nih.gov/NLST) in September 2002. NLST has fully accrued 50,000 current and former smokers (aged 55-74) into a prospective trial, randomizing participants to receive annual spiral CT or annual chest x-rays. Survival data will not be available for a number of years.

The efficacy of lung cancer screening is also being evaluated as part of the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO). Men and women were randomized to receive annual chest x-ray vs usual care. Eligibility was not based on risk of lung cancer because given the large size of the study (> 100,000 participants), it was expected that there would be appreciable numbers of current and former smokers among the participants.

The lack of demonstrated benefit for the older screening approaches should not be misinterpreted as nihilism about the early detection of patients with lung cancer. Individuals at risk (current and former smokers) who present with symptoms consistent with lung cancer deserve appropriate evaluation. The lack of resolution of radiographic abnormalities on a chest x-ray obtained after the

completion of empiric antibiotic therapy for pneumonia should prompt further evaluation for possible lung cancer.

Chemoprevention

Second primary lung tumors develop at a rate of 1%-3% annually for the first 5 years following resection of stage I NSCLC. The retinoid 13-*cis*-retinoic acid (isotretinoin [Accutane]) has reduced the incidence of second primary cancer in head and neck cancer patients in one small randomized trial.

The intergroup randomized trial that assessed the ability of 13-*cis*-retinoic acid to prevent the occurrence of a second primary cancer in patients with completely resected stage I NSCLC showed no impact of treatment on the incidence of second primary tumors. Furthermore, patients who continued to smoke and who received isotretinoin had a higher risk of recurrence of their index cancer. The early findings have demonstrated a higher-than-expected recurrence rate in patients with early-stage lung cancer who received 13-*cis*-retinoic acid and continued to smoke. Also, there was no reduction in second primary tumors in the 13-*cis*-retinoic acid-treated group.

Educational programs Although the information from the intergroup randomized chemoprevention study is being collected, it is important to continue educational efforts to prevent adolescents from starting to smoke cigarettes and to advocate smoking cessation in active smokers. Some experts believe that educational programs must begin during childhood, probably between the ages of 6 and 10 years.

Signs and symptoms

The clinical manifestations of lung cancer depend on the location and extent of the tumor. In patients who have localized disease, the most common symptoms are related to obstruction of major airways, infiltration of lung parenchyma, and invasion of surrounding structures, including the chest wall, major blood vessels, and viscera.

Cough is a major manifestation of lung cancer and is present in nearly 80% of patients with symptomatic lung cancer. It is important to remember, however, that most lung cancer patients are current or former smokers and may have a cough related to chronic irritation of the upper and/or lower airways from cigarette smoke. Therefore, smokers should be asked whether there has been a change in their cough, such as an increase in frequency or severity.

Dyspnea and hemoptysis Increasing dyspnea and hemoptysis may be signs of lung cancer. Although in the case of hemoptysis, 70% of patients are bleeding from nonmalignant causes, mostly infection and more frequently bronchitis. In patients who present with hemoptysis, are older than age 40, and have a history of smoking and chronic obstructive pulmonary disease without abnormality on chest radiograph, lung cancer should be considered in the differential diagnosis.

Pneumonia Postobstructive pneumonia secondary to partial or complete bronchial obstruction occurs relatively frequently in association with lung cancer. It is important to obtain repeat chest x-rays in adults who have been treated for pneumonia to be certain that the radiographic abnormalities have cleared completely.

Pleural effusion Lung cancer may spread to the pleural surface or may obstruct segmental or lobar lymphatics, resulting in pleural effusion and increased dyspnea.

Chest pain Approximately 5% of lung tumors invade the chest wall. The resultant pain is a better predictor of chest wall invasion than are chest CT findings. An individual who complains of persistent chest pain should have a chest x-ray to exclude the presence of peripheral lung cancer that has invaded the chest wall.

Shoulder and arm pain Apical tumors that infiltrate surrounding structures (also called Pancoast's tumors) produce shoulder and/or arm pain as a result of brachial plexus compression. Tumors in the apical lung segments may be difficult to detect on a routine chest x-ray; therefore, a person who complains of persistent shoulder pain, particularly with signs of neurologic involvement, should have a CT scan of the chest to look for an apical tumor. An MRI scan of the chest apex may be beneficial. It is also important to examine the lung apex in bone films obtained to evaluate shoulder pain.

Horner's syndrome Invasion of the sympathetic ganglion by an apical lung tumor causes Horner's syndrome (ptosis, myosis, and ipsilateral anhidrosis).

Hoarseness secondary to vocal cord paresis or paralysis occurs when tumors and lymph node metastases compress, cause dysfunction in, or invade the recurrent laryngeal nerve. This situation is more common on the left side, where the recurrent laryngeal nerve passes under the aortic arch, but it may also occur with high lesions on the right side of the mediastinum.

Other symptoms of tumor compression Lung tumors may also cause dysphagia by compression or invasion of the esophagus or superior vena cava syndrome by compression or invasion of this vascular structure.

Some tumors may result in wheezing or stridor secondary to compression or invasion of the trachea and may also cause signs of cardiac tamponade secondary to involvement of the pericardial surface and subsequent accumulation of pericardial fluid.

Signs and symptoms of metastatic disease Lung cancer can metastasize to multiple sites, most commonly to bone, liver, brain, lungs (contralateral or ipsilateral), and adrenal glands.

Lung cancer patients who have brain metastases may complain of headaches or specific neurologic symptoms, or family members may notice a decrease in the patients' mental acuity. Also, metastatic lung cancer may cause spinal cord compression, resulting in a characteristic sequence of symptoms: pain, followed by motor dysfunction, followed by sensory symptoms. The patient may have any or all of these symptoms.

Patients who complain of bandlike pain encircling one or both sides of the trunk may have spinal cord compression. In addition, coughing and sneezing may cause significant exacerbation of pain from spinal cord compression.

Bone x-rays and/or a bone scan are warranted in lung cancer patients who complain of persistent pain in the trunk or extremities. If performed in the evaluation of lung cancer, ^{18}F-fluorodeoxyglucose (FDG)-PET supplants the need for bone scanning in most patients. PET appears to be more sensitive but less specific for bone metastases. If plain films are normal or equivocal for metastases, CT and/or MRI may be helpful to evaluate suspicious areas. MRI of the spine is the most effective way to evaluate suspected spinal cord compression.

Systemic paraneoplastic symptoms Lung cancer is commonly associated with systemic manifestations, including weight loss (with or without anorexia). In addition, patients frequently complain of fatigue and generalized weakness. SCLC is associated with hormone production, which causes endocrine syndromes in a subset of patients, such as SIADH (syndrome of inappropriate antidiuretic hormone secretion) and via secretion of ACTH (adrenocorticotropic hormone) hypercortisolism.

Specific neurologic syndromes, such as Lambert-Eaton syndrome (see chapter 45), cortical cerebellar degeneration, and peripheral neuropathy, may occur in lung cancer patients but are relatively rare.

Clubbing Although clubbing may occur in a variety of conditions, it is important for the clinician to evaluate a patient's hands. If clubbing is noted, obtaining a chest x-ray may result in the early diagnosis of lung cancer.

Hypertrophic osteoarthropathy A relatively small percentage of patients with lung cancer may present with symptomatic hypertrophic osteoarthropathy. In this syndrome, periosteal inflammation results in pain in affected areas, most commonly the ankles and knees.

Carcinoid syndrome is extremely uncommon in patients who have a bronchial carcinoid tumor. Most of these patients are asymptomatic (tumors are found by x-ray), and a few have cough from an endobronchial lesion.

TUMOR BIOLOGY

Non–small-cell tumors account for approximately 80% of all lung cancers. The three major tumor types included under this category are adenocarcinoma, squamous cell carcinoma, and large-cell carcinoma.

Staging and prognosis

Staging

The staging of lung cancer must be conducted in a methodical and detailed manner. The TNM staging system, updated by Mountain (Table 1), applies equally well to all histologies of NSCLC, but TNM for SCLC is less helpful. Most patients have advanced disease at the time of presentation.

Stage is commonly reported as either clinical or pathologic, designated as c or p, respectively. Clinical stage is based on noninvasive (or minimally invasive) tests, whereas pathologic stage is based on tissue obtained during surgery (see section on "Diagnosis and staging evaluation").

Prognostic factors

Stage The most important prognostic factor in lung cancer is the stage of disease.

Performance status and weight loss Within a given disease stage, the next most important prognostic factors are performance status and recent unexplained weight loss. The two scales used to define performance status are the Eastern Cooperative Oncology Group (ECOG) performance status system and the Karnofsky system (see Appendix 1). Simply, patients who are ambulatory have a significantly longer survival than those who are nonambulatory. Similarly, patients who have lost > 5% of body weight during the preceding 3-6 months have a worse prognosis than patients who have not lost a significant amount of weight.

Molecular prognostic factors Several studies published over the past decade have indicated that mutations of *ras* proto-oncogenes, particularly K-*ras*, portend a poor prognosis in individuals with stage IV NSCLC. Accordingly, research has focused on developing molecularly targeted therapeutic approaches to the *ras* proto-oncogenes, in particular, the farnesyl transferase inhibitors (see section on "Promising novel agents").

Of equal relevance was the completion of large studies by Pastorino et al and Kwiatowski et al evaluating the prognostic importance of immunocytochemical and molecular pathologic markers in stage I NSCLC. The findings of these two studies suggest that pathologic invasion and extent of surgical resection may yield the most critical prognostic information, but mutation of the K-*ras* oncogene and absence of expression of the H-*ras* p21 proto-oncogene may augment the pathologic information.

Diagnosis and staging evaluation

History and physical examination

The diagnosis and preoperative staging of lung cancer begin with a good history and physical examination. When obtaining the history, the clinician should keep in mind the tendency for lung cancer to involve major airways and other central structures. Similarly, the patterns of metastatic dissemination and systemic manifestations must be considered when conducting the physical examination.

Patients should be questioned specifically about the presence of palpable masses, dysphagia, bone pain, headache, or changes in vision. Careful auscultation and percussion may suggest the presence of atelectasis or pleural effusion. Auscultation of the chest also may provide evidence of large airway obstruction and pulmonary consolidation. Ronchi and wheezing may provide some helpful treatment planning information. An enlarged liver may indicate hepatic metastases.

TABLE 1: TNM staging of lung cancer

Primary tumor (T)

Tx	Tumor proven by the presence of malignant cells in bronchopulmonary secretions but not visualized roentgenographically or bronchoscopically or any tumor that cannot be assessed, as in pretreatment staging
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor ≤ 3.0 cm in greatest dimension, surrounded by lung or visceral pleura, and without evidence of invasion proximal to a lobar bronchus at bronchoscopy
T2	Tumor > 3.0 cm in greatest dimension, or tumor of any size that either invades the visceral pleura or has associated atelectasis or obstructive pneumonitis extending to the hilar region (but involving less than the entire lung). At bronchoscopy, the proximal extent of demonstrable tumor must be within a lobar bronchus or at least 2.0 cm distal to the carina
T3	Tumor of any size with direct extension into the chest wall (including superior sulcus tumors), diaphragm, or mediastinal pleura or pericardium without involving the heart, great vessels, trachea, esophagus, or vertebral body; or tumor in the main bronchus within 2 cm of, but not involving, the carina
T4	Tumor of any size with invasion of the mediastinum or involving the heart, great vessels, trachea, esophagus, vertebral body, or carina; or presence of malignant pleural effusion (whether cytology positive or negative)

Regional lymph nodes (N)

Nx	Regional lymph nodes cannot be assessed
N0	No demonstrable metastasis to regional lymph nodes
N1	Metastasis to lymph nodes in the peribronchial and/or ipsilateral hilar region, including direct extension
N2	Metastasis to ipsilateral mediastinal and subcarinal lymph nodes
N3	Metastasis to contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph nodes

Distant metastasis (M)

Mx	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Stage grouping

Occult carcinoma	Tx	N0	M0
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T1	N1	M0
Stage IIB	T2	N1	M0
	T3	N0	M0
Stage IIIA	T3	N1	M0
	T1-3	N2	M0
Stage IIIB	Any T	N3	M0
	T4	Any N	M0
Stage IV	Any T	Any N	M1

From Mountain CF: Revisions in the International System for Staging Lung Cancer. Chest 111:1710–1717, 1997.

Palpation of the neck and supraclavicular fossa Discovery of neck and supraclavicular fossa adenopathy may allow both diagnosis and staging, by needle or open biopsy.

Imaging studies

Chest x-rays provide initial helpful information in patients with new respiratory symptoms. Posteroanterior (PA) and lateral chest x-rays are fundamental in assessing the local extent of the primary tumor and also may provide valuable information regarding metastatic disease.

The chest x-ray should be inspected for the presence of a pleural effusion or synchronous pulmonary nodules, and the bones should be examined for evidence of osseous metastases. A widened mediastinum usually indicates metastatic disease within the mediastinal lymph nodes. Comparison with previous x-rays is helpful and well worth the effort expended in their retrieval.

Chest CT, including the entire liver and adrenal glands with 5-10 mm slices, is performed routinely to further define the primary tumor and to identify lymphatic or parenchymal metastases. In a review of 20 studies that assessed the value of CT scan to determine mediastinal lymph node involvement, with an average prevalence of 28%, CT had a pooled sensitivity of 57%, a specificity of 82%, and a negative predictive value (NPV) of 83%. Benign enlargement of mediastinal nodes is more common in patients with postobstructive infection. Histologic confirmation of the presence or absence of tumor within the mediastinal lymph nodes is necessary whenever this information will change treatment recommendations. In patients who are considered surgical candidates, metastatic tumor is found in approximately 15%-20% of mediastinal lymph nodes < 1 cm in greatest diameter.

It is important to remember that patients with persistent symptoms, such as cough and dyspnea, who have a normal chest x-ray may be harboring a central lesion that is not obvious on chest x-ray but can be easily detected by chest CT. Also, as previously mentioned, apical tumors (Pancoast tumors) may be difficult to detect on a chest radiograph but are usually readily apparent on a CT scan.

PET For lung masses, FDG accumulation on PET implies a significant likelihood of malignancy.

Standardized uptake value (SUV) of 2.5 optimizes the sensitivity and specificity of PET in assessing suspicious lung lesions larger than 1 cm. FDG-PET accumulation is not diagnostic for cancer, nor does it exclude a cancer diagnosis. Bronchioalveolar and carcinoid are two cell types that do not readily accumulate FDG. Furthermore, higher SUV lesions do not imply a greater likelihood of cancer; the highest SUVs have been found in inflammatory lesions, such as granulomas and infections.

A review of 18 studies of the utility of PET to assess the mediastinal lymph nodes demonstrated a pooled sensitivity of 84% and a specificity of 89%, with a positive predictive value (PPV) of 79% and an NPV of 93%. Combining the results of CT and PET, the PPV and NPV were 83%-93% and 88%-95%, re-

spectively. Thus, FDG-PET is superior to CT scanning in staging the mediastinal lymph nodes. Fifteen to 20% of patients with a known or suspected diagnosis benefit from a preoperative FDG-PET, because previously unrecognized metastatic disease will be discovered.

Several trials have evaluated the prognostic significance of FDG uptake on PET scan in NSCLC. Utilizing multivariate Cox analysis, these studies noted that SUV, particularly when > 7-10, was an independent prognostic factor.

PET scanning may also prove a valuable tool for evaluation of patients with NSCLC treated with chemoradiotherapy or irradiation. In a study by MacManus et al, the PET response was found to be a powerful predictor of survival.

Adrenal gland The adrenal gland may be the sole site of metastatic disease in as many as 10% of patients with NSCLC. Patients should not be assumed to have metastatic disease and denied a potentially curative operation on the basis of a scan alone. Adrenal masses at least 1 cm that are negative on CT and FDG-PET were found to indicate a low likelihood of malignancy, whereas FDG-PET–positive masses on visual inspection were found to be more likely malignant. Contrast-enhanced MRI-weighted images may assist in achieving a diagnosis. Suspicious adrenal masses should be either biopsied or resected in potentially operable patients to confirm the stage of disease.

Obtaining a tissue diagnosis

The next step is to obtain a histologic or cytologic diagnosis of the radiologically revealed lesion, although preoperative histologic diagnosis need not be obtained in a highly suspicious lung mass without evidence of distant or locoregional metastases (see below).

Central lesions Collecting sputum cytologies for 3 consecutive days provides a cytologic diagnosis for central lesions 71% of the time and for peripheral lesions 49% of the time. A negative sputum cytology result warants further clinical investigation. Flexible bronchoscopy is commonly required to achieve a diagnosis. For central lesions that are exophytic, at least three direct forceps biopsies should be performed to achieve a 74% sensitivity. Washings and brushings add to the sensitivity but by themselves have a sensitivity of 48% and 59%, respectively. Further improved sensitivity is obtained with bronchoscopic fluoroscopically directed transbronchial needle aspiration biopsies. For central lesions, the overall sensitivity for flexible bronchoscopy is 88% in experienced hands.

In addition, bronchoscopy may provide important staging information, such as whether the tumor involves the distal trachea or carina, and may help plan the appropriate operation (lobectomy or sleeve resection vs pneumonectomy). Determining the degree of bronchial involvement assists surgical planning. Bronchoscopy-directed biopsies should be performed to assist in determining the intended line of resection, especially when evaluating for submucosal involvement.

Peripheral lesions Bronchoscopy is less likely to yield a diagnosis in patients with peripherally located lesions. Bronchoscopic ability to make a diagnosis of

TABLE 2: Selective indications for mediastinoscopy

Enlarged N1, N2, or N3 lymph nodes on chest CT scan
FDG-PET–positive mediastinal disease
Centrally located tumors
T2-T4 tumors

malignancy in peripheral lesions is dependent upon the size; for those less than 2 cm, the sensitivity is 33%, and for lesions greater than 2 cm, it is 62%. If a bronchiole is seen traversing or extending to the mass on CT, the sensitivity is reported to be twice as high, nearly 60%.

A CT-guided needle biopsy may diagnose up to 90% of peripheral lung cancers but is dependent on the quality of the CT scan and the experience of the radiologist performing the procedure. The false-negative rate is 20%-30%. Needle biopsy is usually reserved for patients who are not candidates for an operation due to distant metastatic disease or poor health or performance status. If the patient is a candidate for surgery, resection is generally recommended for any suspicious mass whether the result of needle biopsy is positive or nondiagnostic. Therefore, for patients with a suspicious peripheral lesion that is not associated with pleural effusion or mediastinal adenopathy, it is reasonable to proceed directly to surgery.

Mediastinoscopy Mediastinoscopy is a time-tested technique whereby the middle (cervical mediastinoscopy) and the anterior mediastinum may be assessed for direct or metastatic lymph node involvement. In the hands of a specialist, the risk of death; biopsy trauma of local structures such as the great vessels, trachea, or esophagus; bleeding; recurrent nerve paresis; or infection is minimal. Whole-node biopsies may be taken, achieving a great deal of information about the location, degree of nodal involvement, and capsular invasion. There is no evidence that mediastinoscopic biopsy spreads tumor within the mediastinum, worsens the prognosis, or renders eventual surgical mediastinal dissection difficult.

Mediastinoscopy may be performed for the following indications (Table 2): enlarged nodes on CT, positive nodes on PET, centrally located tumors, and T2-T4 tumors. To assess response to therapy, repeat mediastinoscopy has been performed with few complications. Patients with N2 disease may potentially benefit from neoadjuvant treatment. Patients with N3 disease are considered to be stage IIIB and less likely to benefit from surgical resection. There have been a few retrospective reports that have demonstrated survival from induction therapy in patients with microscopic N3 involvement.

Thoracentesis and thoracoscopy Individuals who have pleural effusions should undergo thoracentesis. Video-assisted thoracoscopic surgery (VATS) should be used to assess patients who have cytology-negative effusions. Sixty percent of patients with known pleural disease and effusions will have cytology-negative effusions. However, lung cancer patients with exudative cytol-

ogy-negative effusions and their cytology-positive counterparts appear to have equally poor survival. VATS permits direct visualization of the pleural surface, enables one to directly biopsy pleural nodules, and also may facilitate biopsy of ipsilateral mediastinal lymph nodes. The role of VATS to assess effusions remains to be elucidated.

Measurement of serum tumor-associated antigens has no current role in the staging of NSCLC.

Evaluation for distant metastases

Once a tissue diagnosis has been established, the possibility of distant metastases should be assessed. Again, this process starts with a careful history and physical examination.

Clinical stage I/II patients Patients with clinical stage I or II lung cancers based on chest x-ray and CT scan, no evidence of skeletal or neurologic metastases, and normal blood chemistries and blood counts do not require brain or bone scans.

Symptomatic, clinical stage I/II patients, those who have lost > 5% of their usual body weight, and those who cannot work on a regular basis due to decreased performance status (ECOG performance status ≥ 2), should have a brain scan. An FDG-PET should be performed to assess for metastatic disease as well as to evaluate the primary and the mediastinum.

Clinical stage III patients Patients who have physical findings, laboratory findings, or symptoms suggestive of distant metastases should undergo appropriate scans to evaluate these areas. In addition, most clinical trials of combined-modality therapy for stage III disease require radiologic imaging of the brain and bone.

To reliably assess for metastatic brain lesions, a high-dose gadolinium (double to triple) brain MRI on a greater than 1.5 T machine with appropriate conformal analysis is far superior to a brain CT and should be used in any patient who can tolerate the procedure.

Diagnosis and evaluation of suspected carcinoid tumor

A carcinoid tumor of the lung may be suspected in a patient with a slowly enlarging pulmonary mass and a prolonged history of respiratory symptoms. Patients usually have no symptoms. Most tumors are located centrally and exist endobronchially. When they occur, symptoms may include wheezing, recurrent pneumonia, dyspnea, and potentially paraneoplastic syndromes. Bronchoscopy frequently assists in diagnosing the lesion. The finding of a polypoid, pale, firm mass should not lull the bronchoscopist into taking a large-forceps biopsy. First, these masses are frequently vascular, and massive bleeding has been reported; second, the entire mass can be accidentally removed, making it difficult to identify the location of the orgin of the polyp.

Given the bleeding potential, rigid bronchoscopy may be a better way to assess these lesions. Especially with cytology, carcinoid tumors may be difficult to differentiate from small-cell and atypical carcinoid tumors. Carcinoid tumor

should be suspected when a small-cell tumor diagnosis by fine-needle aspiration does not respond to therapy. True carcinoids will have metastatic nodal disease in 5%-10% of patients and have an excellent prognosis with surgical resection. Atypical carcinoid tumors are differentiated from typical tumors in that they have more than two mitotic figures per high-powered field and areas of necrosis.

Unlike its infradiaphragmatic counterpart, pulmonary carcinoid tumors rarely present with paraneoplastic syndromes, including carcinoid, acromegaly, and Cushing syndromes. Therefore, it is only necessary to measure urinary 5-hydroxyindoleacetic acid (5-HIAA) excretion prior to surgery in symptomatic patients. Fewer than 3% of all patients with pulmonary carcinoid tumors can be found to have any detectable urinary 5-HIAA.

Intraoperative staging

Intraoperative staging is an integral part of any operation for lung cancer. In addition to the thorough visual and tactile inspection of the lungs, diaphragm, and pleura, the ipsilateral mediastinal lymph nodes must be either completely removed or, at a minimum, sampled.

The American Thoracic Society has assigned numbered levels to locations in which lymph nodes are regularly found, defined by their relation to constant anatomic structures. For instance, 4R lymph nodes are those that are found between the cephalic border of the azygous vein and the caudal border of the innominate artery where it crosses the trachea. A complete mediastinal lymph node dissection is associated with little morbidity and lengthens the operation only slightly.

Pulmonary evaluation

To determine the volume of lung that can be removed without rendering the patient a pulmonary cripple and to identify those individuals at risk for postoperative complications, each patient may undergo pulmonary function testing, spirometry, and potentially a diffusing capacity. The results of pulmonary testing should be referenced to the normal values for ethnicity, height, age, and sex.

Forced expiratory volume in 1 second Postoperative respiratory failure rarely occurs if the postresection forced expiratory volume in 1 second (FEV_1) is > 800 mL or > 30% of predicted. Regardless of the extent of the scheduled resection, if the preoperative FEV_1 is < 2 L or < 60% of predicted, a split-function perfusion scan should be obtained to determine the contribution of each lung to overall pulmonary function. This information may be critical when an unplanned pneumonectomy is required to achieve complete tumor resection.

Other pulmonary function tests A diffusing capacity of the lung for carbon monoxide (D_LCOa; a= adjusted for the patient's hemoglobin) < 60% of the predicted value or a maximum voluntary ventilation (MVV) < 35% is associ-

ated with increased postoperative morbidity. Patients with a baseline oximetry saturation of less than 90% and those who desaturate with exercise more than 4% have a greater likelihood of postoperative complications. Arterial blood gas $pCO_2 > 45$ mm Hg is an independent risk factor for increased operative morbidity and mortality.

In patients with borderline lung function, further physiologic testing may be required to better estimate pulmonary reserve prior to and after surgery. Quantitative pulmonary effusion scanning may assist in this endeavor. The perfusion portion is used to calculate the percentage of lung to be removed and the estimated postoperative percentage of normal. An additional test is exercise pulmonary function testing. Patients are monitored for heart rate, rhythm, blood pressure, and oxygen consumption. Patients who reach their target heart rate and exercise capacity and who have a maximal oxygen consumption > 15 mL/kg/min are less likely to have a postoperative complication.

Pathology

The World Health Organization and the International Association for the Study of Lung Cancer have devised guidelines for the histologic classification of lung cancer, which are revised as necessary (Table 3). The different cell-type classifications are performed using light microscopy and do not require electron microscopy or immunohistochemistry. There are variations in the natural history of the different cell types and potential differences in response to treatment and survival. Overall, 90%-95% of NSCLC is adenocarcinoma, squamous, or large cell, with 3%-4% being mixed tumors, such as adenosquamous carcinoma. Three major types of tumors are included under the NSCLC category: adenocarcinoma, squamous cell carcinoma, and large-cell carcinoma.

Adenocarcinoma is the most common type of NSCLC, accounting for approximately 30%-40% of cases. Of all the types of lung cancer, adenocarcinoma is most likely to occur in nonsmokers or former smokers. It is also the most common tumor in women.

Typically, adenocarcinoma presents as a small peripheral lesion that has a high propensity to metastasize to both regional lymph nodes and distant sites. Because of the tendency of the primary tumor to occur in peripheral locations, it frequently produces no symptoms. In contrast with their metastatic lesions, the primary adenocarcinoma tumor is histologically heterogeneous in 80% of patients, consisting of numerous histologic subtypes, and is classified as "mixed-" or "indeterminate-adenocarcinoma."

Bronchioloalveolar adenocarcinoma (BAC) During the past decade, it has become apparent that the incidence of BAC is increasing. This tumor originates from type II pneumocytes, and it may present as a pneumonic infiltrate, as multiple nodules scattered throughout the lungs, and, occasionally, as a single nodule.

Squamous cell tumors comprise approximately 30% of all cases of lung cancer. These tumors tend to occur in a central location and tend to spread to regional lymph nodes; they are the most likely of all lung cancers to remain

localized and to cavitate. In fact, autopsy studies have shown that about 15%-30% of patients with squamous cell carcinoma may die of local disease without evidence of distant metastases.

Large-cell carcinoma accounts for approximately 10%-15% of all lung cancers. It tends to present as a relatively large peripheral lesion, and, like adenocarcinoma, has a high propensity to metastasize to regional lymph nodes and distant sites.

Treatment

In operable candidates, clinically staged IA, IB, IIA, and IIB NSCLC should undergo anatomic complete surgical resection. Primarily, patients with stage IIIB and IV disease are treated nonoperatively. Although multimodality therapy is routinely recommended for stage IIIA disease, it is recommended that it be performed within a clinical trial.

SURGICAL APPROACH

The appropriate treatment of NSCLC is resection of the lobe containing the tumor. Occasionally, a bilobectomy or pneumonectomy is required. Mortality approximates 3% following lobectomy and 7% following pneumonectomy. A wedge or segmental resection has a three to five times higher incidence of local recurrence and a lower 5-year survival than a lobectomy. Therefore, if the patient can tolerate the procedure, the standard operation should be a lobectomy, rather than a wedge resection or segmentectomy. Segmentectomy, though, was not studied separately from wedge resection, and more recent evaluation demonstrates that in selected tumors, when the bronchus and vascular supply are individually ligated with a regional node resection, survival appears to be comparable, yet salvages lung parenchyma.

VATS Traditionally, lung cancers have been resected through a posterolateral thoracotomy incision. Muscle-sparing incisions may reduce pain. The current trend is toward an even less invasive approach: lobectomy and lymph node dissection with VATS. This approach appears to offer the same cancer operation and survival with perhaps lower morbidity.

Two VATS methods have been described: the mass hilar ligation technique and individual ligation of the vasculature and airway. Patients with peripheral tumors up to 4-6 cm without clinical hilar or mediastinal adenopathy appear to be good candidates for a VATS procedure. Conversion rates to open thoracotomy are 10%, and hospital stays are usually 3-5 days.

The results of several VATS series show lower complication rates than reported series for thoracotomy, granted a selection bias may have occurred. One small randomized trial showed a significant benefit favoring VATS. Patients have better shoulder function, better performance on the 6-minute walk, and less impairment of vital capacity after VATS than after a thoracotomy. A VATS approach may be better tolerated than other approaches for older patients.

Patients with pathologic stage IA disease have a 70%-80% 5-year survival rate

TABLE 3: WHO and IASLC guidelines for the histologic classification of lung cancer

I	**Adenocarcinoma**
	i. Adenocarcinoma with mixed subtypes
	1. Well-differentiated fetal adenocarcinoma
	2. Mucinous adenocarcinoma
	3. Mucinous cystadenocarcinoma
	4. Clear cell adenocarcinoma
	5. Signet ring adenocarcinoma
	ii. Acinar
	iii. Papillary
	iv. Bronchioloalveolar carcinoma
	1. Mucinous
	2. Nonmucinous
	3. Mixed mucinous and nonmucinous
	v. Solid adenocarcinoma with mucin
II	**Squamous**
	i. Papillary
	ii. Small-cell
	iii. Clear cell
	iv. Basaloid
III	**Large-cell**
	i. Large cell neuroendocrine carcinoma
	ii. Basaloid carcinoma
	iii. Lymphoepithelioma-like carcinoma
	iv. Mixed large-cell neuroendocrine carcinoma
	v. Clear cell carcinoma with rhabdoid phenotype
IV	**Adenosquamous carcinoma**
V	**Carcinomas with pleomorphic, sarcomatous characteristics**
	i. Carcinosarcoma
	ii. Pulmonary blastoma
	iii. Carcinomas with spindle and/or giant cells
	1. Giant cell carcinoma
	2. Spindle cell carcinoma
	3. Pleomorphic carcinoma
	iv. Other
VI	**Carcinoid**
	i. Typical carcinoid
	ii. Atypical carcinoid
VII	**Carcinomas of salivary gland origin**
	i. Adenoid cystic carcinoma
	ii. Mucoepidermoid carcinoma
	iii. Others
VIII	**Unclassified**

Adapted from the World Health Organization. Histologic typing of lung tumors. In: International Classification of Tumors. Geneva, Switzerland: WHO, 1991; Travis WD, Colby TV, Corrin B, et al: World Health Organization: Histological Typing of Lung and Pleural Tumours, 3rd ed. Berlin: Springer-Verlag, 1999.

after resection, whereas 5-year survival rates are 60% in those with stage IB disease and 40%-50% in those with stage IIA/IIB disease. Patients found to have N2 (stage IIIA) disease located at a single nodal level have a 25%-30% 5-year survival rate.

Mediastinal lymph node involvement The standard lung cancer operation should include sampling or dissection of mediastinal lymph nodes. The presence of metastases in any of the mediastinal lymph nodes (N2 and/or N3 disease) is indicative of advanced disease and is thought by some to represent a contraindication to surgery. Resection of mediastinal disease may have prognostic significance, implications for postoperative care, and potential therapeutic value. Some series of patients with N2 disease have shown a 5-year survival rate of 20%-30%, but patients in these series are highly selected.

The American College of Surgeons has completed accrual to a randomized, prospective study comparing survival following mediastinal lymph node sampling vs dissection. Data are still being collected. Also, clinical trials are currently testing preoperative chemotherapy and chemoradiation therapy in patients with mediastinal node involvement.

Preoperative histologic assessment of the mediastinal lymph nodes is essential if multilevel metastases are suspected, as there have been few long-term survivors among patients with metastatic disease at more than one level. Nonsurgical treatment appears preferable, or patients should be offered participation in a trial designed to assess the benefits of neoadjuvant therapy. Although patients with stage IIIB tumors are usually treated with irradiation and chemotherapy (see later discussions), the occasional patient with isolated involvement of the vena cava or atrium can undergo resection.

Carcinoid tumors Although the majority of carcinoid tumors remain localized, regional lymph node metastases are identified in 5%-15% of patients. The surgical approach, therefore, should be similar to that used in NSCLC. If a small tumor in a proximal airway is identified and there is no histologic evidence of lymph node disease, a bronchoplastic procedure with preservation of lung tissue can sometimes be performed. Rates of survival at 10 years are > 90% for patients with stage I disease and 60% for patients with stage II disease.

ADJUVANT THERAPY

Chemotherapy

Classic postoperative adjuvant chemotherapy has been tested in three randomized trials conducted by the Lung Cancer Study Group (LCSG). For almost 20 years, the relative value of adjuvant chemotherapy for resectable NSCLC has been disputed and debated. In a randomized, prospective study involving 488 patients, Keller et al showed no benefit to adjuvant chemotherapy. The ALPI (Adjuvant Lung Project Italy) study of 1,209 patients also showed no survival benefit. In contrast, the International Adjuvant Lung Cancer Trial (IALT) randomized 1,867 patients to receive cisplatin-based, adjuvant chemotherapy or no treatment. At 5 years, the treatment arm showed a survival advantage of 4.1% ($P = .003$), compared with the observation arm.

Two recently presented trials, the Canadian BR-10 and Cancer and Leukemia Group B (CALGB) 9633, both demonstrated clinically significant improvement in survival, with minimal chemotherapy side effects; cisplatin and vinorelbine were used in the BR-10 trial and carboplatin and paclitaxel were

used in CALGB 9633. These results, in combination with the recent positive findings of the adjuvant trial of UFT (a drug composed of tegafur and uracil mixed at the ratio of 1:4) in patients with stage IB NSCLC, increase the likelihood of adjuvant platinum-based therapy becoming the standard of treatment for patients with stages IB-IIIB NSCLC.

Further data from two subsequent positive adjuvant chemotherapy trials support this new standard. Based on these data, the standard of practice has shifted to chemotherapy for operable NSCLC, either adjuvant or in the induction setting. The potential benefits are higher efficacy of chemotherapy early in the natural history of disease, facilitation of subsequent local therapy, and early eradication of distant micrometastases. Despite these positive data, not all patients benefit from adjuvant chemotherapy.

Stage I disease In one trial, adjuvant therapy with six courses of CAP (cyclophosphamide [Cytoxan, Neosar], Adriamycin [doxorubicin], and Platinol [cisplatin]) failed to produce a significant survival advantage in patients with stage I lung cancer. The IALT demonstrated that modern adjuvant chemotherapy could be provided with a survival advantage. In patients with stage IB disease, CALGB 9335 compared postoperative carboplatin and paclitaxel with surgery alone and found a clinically and significant survival advantage, with minimal morbidity. The Canadian BR-10 trial demonstrated similar results using cisplatin and vinorelbine; patients with stage II disease were included as well.

The current trend is to provide continued observation for stage I patients and involvement in a chemopreventive clinical trial for stage IA patients. For patients with stage IB disease, platinum-based adjuvant chemotherapy (cisplatin or carboplatin combined with a taxane or vinorelbine) should be strongly considered.

Stage II/III disease In two earlier trials, postoperative adjuvant chemotherapy with six courses of CAP, given alone in one study and following postoperative radiation therapy in the other, resulted in a modest improvement in median survival but had no impact on long-term survival. In contrast, the IALT and Canadian BR-10 trials demonstrated a clinically significant survival advantage, justifying consideration for adjuvant chemotherapy. There does not appear to be any survival advantage to adding adjuvant mediastinal radiotherapy to chemotherapy, unless there are particularly high risk factors for local recurrence.

Radiation therapy

A trial conducted by the LCSG showed that in patients with squamous cell carcinoma of the lungs and resected N1/N2 disease, administration of postoperative radiation reduced the risk of recurrence in the chest from 20% to 1%. Although there was no improvement in overall survival, postoperative irradiation was associated with a significant improvement in disease-free survival for patients with N2 disease. A trial by the British Medical Research Council reached similar conclusions. In contrast, a prospective, randomized European trial comparing 60 Gy of adjuvant radiation therapy with surgery alone found a survival advantage for the surgery-only arm (50% vs 24%), with no difference in local control.

The preliminary results of the intergroup trial 0139 (RTOG 93-09) have been reported. In this trial, 429 patients with pathologic N2 (stage IIIA) disease were randomized to receive either induction chemoradiation therapy (cisplatin and etoposide and 45 Gy) followed by surgical resection vs definitive chemoradiation therapy (cisplatin and etoposide and 61 Gy). The pathologic complete response rate on the surgical arm was 36%. More treatment-related deaths occurred on the surgical arm (7% vs 1.6% on the chemoradiation arm). The 3-year disease progression-free survival was superior on the surgical arm (29% vs 19%, $P = .02$). The median survival for each arm was 22 months ($P = .51$). There were more early noncancer deaths on the surgical arm, but overall survival curves crossed so that by year 3, overall survival was 15% better on the surgical arm (absolute: 38% vs 33%). Longer follow-up will be needed to determine whether surgery significantly prolongs survival in patients with stage III (pN2) NSCLC (*Albain KS, Scott CB, Rusch VR, et al: Proc Am Soc Clin Oncol [abstract] 22:621, 2003).*

These results created a lack of consensus about treatment recommendations, with some experts advocating the use of postoperative radiation therapy to reduce local recurrence, and others avoiding it because of the absence of an effect on survival.

A meta-analysis of nine randomized trials assessing postoperative radiation therapy in lung cancer reported a 21% increase in mortality in patients receiving this therapy. However, many of the patients in these trials had N0 disease, for whom few would advocate radiation therapy. Also, most of the patients were treated with cobalt-60 beams and technically limited treatment planning, not with modern radiation therapy techniques.

At present, therefore, the appropriate role of postoperative radiation therapy remains controversial. Such therapy should be seriously considered, however, in patients at high risk for locoregional relapse (ie, those with hilar or mediastinal disease, squamous histology, multiple positive lymph nodes or lymph node stations, extracapsular extension, bulky nodal disease, or close or microscopically positive margins). In patients who are receiving adjuvant chemotherapy, it is reasonable to administer the chemotherapy first (as it has been associated with a survival benefit) followed by radiation therapy (for enhanced local control).

Moreover, in a randomized trial by Keller et al, no benefit was shown for concurrent chemoradiation over radiation therapy when in the adjuvant setting for completely resected patients with stage II/IIIA NSCLC. An exception may be in patients with microscopic residual disease (ie, positive margins or extracapsular extension), for whom a delay in radiation therapy may be detrimental. Radiotherapy may be less advantageous if provided more than 6-7 weeks after surgery, and a higher rate of complication is expected in elderly patients with numerous comorbidities, such as chronic obstructive pulmonary disease.

NEOADJUVANT CHEMOTHERAPY OR CHEMORADIATION THERAPY

During the past decade, numerous phase II trials showed that, in general, it is feasible to perform pulmonary resection following chemotherapy or chemoradiation therapy. Although surgery can be more difficult after preoperative treatment, morbidity and mortality were acceptable.

Stage IIIA/IIIB disease The greater effectiveness of current chemotherapeutic regimens to reduce disease bulk suggested that their use prior to surgery, either alone or in combination with radiation therapy, might increase both resectability and survival in patients with stage IIIA NSCLC. Multiple phase II trials have shown such an approach to be feasible; however, it is not clear that such a strategy improves median or long-term survival over best nonsurgical chemoradiotherapy among patients who initially have more than minimal N2 disease.

Based on these initial observations, three groups conducted small randomized trials testing preoperative therapy. Two of these studies showed significantly improved survival among patients who received three courses of cisplatin-containing chemotherapy prior to surgery. In the third trial (reported in abstract form only), Brazilian investigators observed significantly higher rates of resection and significantly longer survival in patients who received preoperative chemoradiation therapy than in those given preoperative chemotherapy alone.

In an analysis of 686 patients who underwent surgical resection of N2 NSCLC, preoperative chemotherapy was associated with a better survival outcome in a subgroup of patients with clinically evident N2 disease ($P < .0001$) than in those who did not receive preoperative chemotherapy. The 5-year survival rate was 18% for patients treated with preoperative chemotherapy, compared with 5% for those not treated.

Current recommendations In selected patients, preoperative treatment may have a favorable effect on outcome in surgically resectable stage IIIA NSCLC. Although aggressive neoadjuvant approaches may have treatment-associated mortality in the range of 5%-12%, in experienced institutions, potential benefits seem to outweigh the risks. The results of the intergroup randomized trial (see box) comparing preoperative chemoradiation therapy with definitive chemoradiation therapy (in pathologic N2 disease) showed a significant improvement in disease progression-free survival (but not overall survival) in the surgical arm ($P = .02$). Patients with persistently positive N2 disease after induction therapy do not appear to benefit from resection.

Stage I-IIIA disease Neoadjuvant chemotherapy may even play a role in early-stage disease. A multicenter trial from France randomized 373 stage I-IIIA NSCLC patients to undergo either surgery alone or chemotherapy (mitomycin [Mutamycin, 6 mg/m^2 on day 1], ifosfamide [Ifex, 1.5 g/m^2 on days 1-3], and cisplatin [30 mg/m^2 on days 1-3]) at 3-week intervals for three cycles followed by surgery. Disease-free survival was significantly longer in the patients randomized to receive neoadjuvant chemotherapy than in those treated with surgery alone ($P = .02$). The most striking benefit of chemotherapy was seen in patients who had minimal lymphadenopathy (either N0 or N1, $P = .008$). No excessive complications were seen in the chemotherapy-treated patients.

A phase III trial comparing neoadjuvant chemotherapy with paclitaxel/carboplatin vs surgery alone in early-stage NSCLC (the Bimodality Lung Oncology Team [BLOT] vs NOT study) did not reach accrual, and the results are being analyzed. The phase II 3-year survival rates of 64% with this strategy appear promising.

SPECIAL CIRCUMSTANCES

Chest wall invasion and/or bulky hilar disease

Invasion of the chest wall has a poorer prognosis than invasion of the parietal pleura. Patients with chest wall invasion may present with chest wall pain, either constant or pleuritic. Confirmation of chest wall involvement is associated with the presence of pain in the location of involvement, visualization of the tumor transgressing normal chest wall plains, or the demonstration of rib destruction/involvement on plain radiograph, CT, MRI, or bone scan. Patients presumed or found to have chest wall involvement should undergo a full metastatic evaluation, including a chest CT, FDG-PET, brain MRI, and mediastinoscopy. Pretreatment thoracoscopy may be helpful to assess the degree of chest wall and pleural space involvement.

Bulky hilar disease should be evaluated similarly, given the high prevalence of clinically unrecognized metastatic disease in these patients. Furthermore, bronchoscopy is often helpful to detect an endobronchial component, evaluate the bronchial anatomy (given the possibility of carinal or sleeve resection), determine the presence of synchronous or metastatic cancer, and assess submucosal spread to determine the potential line of bronchial resection.

Preoperative radiation or chemoradiation therapy may decrease the tumor bulk and thus decrease the amount of vital tissue necessary for complete resection. In the case of a hilar mass, removing a lobe rather than performing a pneumonectomy will reduce the operative mortality by more than 50%. Radiation doses of 30-64 Gy have been used along with radiation chemosensitizers.

T4 N0/1 (nonpleural disease) tumors

Some patients with T4 disease may be surgical candidates and thus have a curative potential. The more commonly involved structures are the carina, left atrium, superior vena cava, vertebral body and aorta. Patients should be thoroughly evaluated for metastatic disease. Those who are not surgical candidates may be considered for chemoradiotherapy without surgery, with a survival rate of approximately 10%-15%.

Satellite nodules

Satellite nodules may occur within the same lobe, a different lobe, or the opposite lung. For patients who have undergone complete resection and possess a satellite nodule within the same lobe and no nodal involvement, survival is between 54% and 70%, nearly the same as for patients with stage I disease without a satellite nodule. However, the survival is significantly worse with a satellite nodule in a separate lobe, with a 5-year survival rate averaging 10%. Most CT-identified satellite lesions in patients with NSCLC are benign. Thus, there should be no attempt to preoperatively diagnose the second lesion in patients with a satellite nodule in the same lobe, but investigation should be considered when satellite leisons are found in different lobes. It is inappropriate to assume that there is metastatic disease.

For patients with suspicious lesions in other lobes or on opposite sides of the chest, there should be a thorough metastatic evaluatinon. In fact, the likelihood that the second lesion is benign or there is a second primary is higher than that of an isolated pulmonary metastasis. In these patients, a core-needle biopsy with histologic confirmation should be performed.

These patients should undergo preoperative chest CT, FDG-PET, and potentially brain MRI to rule out the possibility of metastatic disease. They should then undergo thorough mediastinal evaluation, given the increased likelihood of mediastinal involvement. If the nodules are operable and the histologies appear to be different, complete resection of each of the two separate primaries can be performed, preserving the pulmonary parenchyma. Segmentectomy and even possibly wedge resection may be necessary, although not ideal. The prognosis is associated with the stage of the more advanced of the two primaries and is slightly worse than that for patients with nonsynchronous disease, stage for stage.

Brain metastases

The brain is one of the more common sites of metastatic disease in NSCLC. The median survival in patients treated with steroids alone is approximately 2 months and in those with whole-brain radiation therapy, 6 months. Surgical resection of brain metastases and the primary lung cancer may be considered in selected patients. A thorough evaluation for other metastatic disease should be performed with a chest CT scan, FDG-PET, and an additional brain MRI if the patient has had a brain CT scan. If there is no evidence of metastatic disease, the patient should undergo mediastinoscopy to determine whether there is N2 or N3 disease. If surgery is performed, it should be an R-0 resection to achieve a survival advantage.

Stereotactic radiotherapy may be an alternative to brain surgery, with a similar cure rate. Usually, patients with three or fewer lesions that are peripheral, supratentorial, less than 3 cm, and mediastinal node-negative are more likely to benefit from surgical resection of the brain metastasis(es) and the primary. The role of whole-brain radiation therapy (WBRT) in these patients is controversial, given the morbidity associated with WBRT and the fact that less than half of patients will have further brain recurrence after adequate treatment. Furthermore, the quality of MRI allows for close and detailed follow-up, permitting early detection of recurrence or other new lesions.

The brain lesion should be treated first, and if mediastinoscopy is used, it should precede chemoradiotherapy. The role of induction chemoradiotherapy before lung resection is controversial. The determination and the amount of lung reesected should be the same as those for nonmetastatic patients. The 5-year survival rate is between 16% and 30%.

TREATMENT OF PATIENTS WITH MEDICALLY INOPERABLE STAGE I/II DISEASE

Some patients with resectable stage I or II NSCLC are high-risk operative candidates because of poor cardiopulmonary function or other medical problems. Other patients refuse to undergo surgery despite the recommendation of their treating physicians. In such patients, an attempt should be made to optimize pulmonary function by encouraging smoking cessation and initiating vigorous treatment with bronchodilators, corticosteroids, and antibiotics.

Radiation therapy

Several institutions have reported their experience with definitive radiation therapy for such patients. Although the results are not as good as those reported in patients selected for surgery (possibly due to differences in patient selection and between clinical vs pathologic staging), patients with medically inoperable early-stage NSCLC clearly should be offered radiation therapy, with reasonable expectation of cure. Timmerman et al reported the results of a phase I study of extracranial stereotactic radioablation (ESR) in patients with medically inoperable stage I NSCLC. ESR was delivered in 3 fractions over 2 weeks, with a starting dose of 800 cGy per fraction. The dose was escalated to 2,000 cGy per fraction for 3 fractions (6,000 cGy total). Of 36 patients, 1 developed grade 3 hypoxemia and another, symptomatic radiation pneumonitis. The maximum tolerated dose was not reached.

Radiofrequency ablation

Patients who are not operative candidates may be treated with radiofrequency ablation (RFA). There is considerable experience with RFA for cancer in other organs, and its use for lung cancer is growing. It can be performed either intraoperatively or percutaneously with CT guidance. The preliminary findings show these radiologic results: complete response (0%), partial response (50%), stable disease (30%), and disease progression (20%).

TREATMENT OF PATIENTS WITH STAGE IIIA/IIIB DISEASE

Radiation therapy

In the past, radiation therapy was considered the standard therapy for patients with stage IIIA or IIIB disease. Long-term survival was poor, in the range of 5%, with poor local control and early development of distant metastatic disease.

Altered fractionation schedules A randomized trial compared standard daily radiation therapy (66 Gy) with a continuous hyperfractionated accelerated radiation therapy regimen [CHART] that delivered 54 Gy over 2½ weeks. The altered fractionation schedule resulted in improved 2-year survival.

Various efforts are under way to look at combining altered fractionation schema with chemotherapy. Although the preliminary results of Radiation Therapy Oncology Group (RTOG) 94-10 do not favor altered fractionation (see section on "Concurrent vs sequential chemoradiation therapy"), the long-term results of another study support this strategy. Jeremic et al compared hyperfractionated

radiation therapy (bid to 69.6 Gy) and concurrent low-dose daily carboplatin/etoposide with or without weekend carboplatin/etoposide in a randomized trial of approximately 200 patients. Although investigators found no benefit with the addition of weekend carboplatin/etoposide, both arms demonstrated promising median survival times of 20 and 22 months and excellent 5-year survival ratios of 20% and 23%.

Conformal radiation therapy

Hayman et al reported updated results of the Michigan phase I dose-escalation trial of three-dimensional (3D) conformal radiation therapy for NSCLC. In this study, the radiation dose was escalated based on the effective volume of irradiated lung (up to 102.9 Gy). Such doses produced acceptable toxicity and no cases of isolated failures in purposely unirradiated, clinically uninvolved nodal regions. This strategy is beginning to be integrated with chemotherapy.

Socinski et al reported a dose-escalation radiotherapy (from 60-74 Gy) trial, using 3D computer-assisted planning techniques, in patients receiving induction carboplatin and paclitaxel and concurrent weekly carboplatin/paclitaxel. Ninety-seven percent (31 of 32) of the patients completed therapy to 74 Gy, as planned. The grade 3/4 esophagitis rate overall was relatively low at only11%. Moreover, the results found a promising median survival of 26 months and 3-year survival of 47%.

Interestingly, investigators at M. D. Anderson Cancer Center found that the maximum tolerated dose (MTD) of gemcitabine (Gemzar) administered weekly concurrent with conventional (two-dimensional) thoracic irradiation was only 125 mg/m^2/wk × 7 weeks vs 190 mg/m^2/wk × 7 weeks utilizing 3D conformal radiotherapy. Further escalation of the radiation therapy dose in the context of chemotherapy will need to be evaluated.

Chemoradiation therapy

Chemoradiation vs radiation therapy alone At least 11 randomized trials have compared thoracic irradiation alone with chemoradiation therapy in patients with stage III NSCLC. Several meta-analyses have demonstrated a small, but statistically significant, improvement in survival with the combined-modality regimens. Indeed, six randomized trials have demonstrated a statistically significant survival advantage favoring chemoradiation therapy: Three of these trials employed sequential chemoradiation therapy and the other three employed concurrent chemoradiation therapy.

In the three trials using sequential chemoradiation therapy, the combination of cisplatin with a vinca alkaloid (either vinblastine or vindesine) significantly improved survival rates over radiation therapy alone.

The first of the concurrent chemoradiation therapy trials, the European Organization for Research and Treatment of Cancer (EORTC) trial 08844, compared radiotherapy alone with radiotherapy and concomitant (daily or weekly) low-dose cisplatin therapy. This study demonstrated a significant survival advantage for daily cisplatin and radiotherapy compared with radiotherapy alone

(3-year survival rates, 16% vs 2%); the weekly cisplatin/radiation therapy arm produced intermediate results (3-year survival rate, 13%).

A three-arm, randomized study comparing hyperfractionated radiotherapy (1.2 Gy twice daily to a total dose of 64.8 Gy) alone with a combination of hyperfractionated radiotherapy and carboplatin plus etoposide (administered weekly or every other week) demonstrated 3-year survival rates of 7%, 23%, and 16%, respectively ($P = .003$).

In the third phase III concurrent chemoradiation therapy trial, the combination of hyperfractionated radiation therapy and low-dose daily chemotherapy (carboplatin plus etoposide) was superior to hyperfractionated radiation therapy alone (to 69.6 Gy), with 4-year survival rates of 22% vs 9% ($P = .02$).

Analyses of these positive randomized trials favoring chemoradiation over radiation therapy alone suggest a difference in the patterns of failure that relates to the method of combining chemotherapy with thoracic radiotherapy. In the three trials employing sequential chemoradiation therapy, the improvement in survival rates over irradiation alone appeared to be linked to a decrease in the development of distant metastases. In contrast, in the three positive trials employing concurrent chemoradiation therapy, the survival advantage appeared to be associated with an improvement in locoregional control.

It may be that the use of high-dose induction chemotherapy combats systemic disease, whereas the simultaneous delivery of low-dose chemotherapy (cisplatin or carboplatin) with irradiation may be necessary to improve local tumor control. Such a construct fits well with prior observations that platinum-based chemotherapy can act as a radiosensitizer.

Concurrent vs sequential chemoradiation therapy Furuse et al evaluated mitomycin, vindesine, and Platinol (MVP), administered either concurrently or prior to thoracic irradiation (56 Gy), in patients with unresectable stage III NSCLC. With over 300 patients randomized, survival favored concurrent over sequential therapy (median survival, 16.5 vs 13.3 months, and 5-year survival rates, 15.8% vs 8.9%; $P = .04$). Furuse et al also reported the patterns of failure, which demonstrated a benefit of concurrent chemoradiotherapy in improving the local relapse-free survival ($P = .04$) but not the distant relapse-free survival ($P = .6$).

Curran et al recently presented the long-term results of a larger randomized trial (> 600 patients) comparing sequential vs concurrent chemoradiotherapy (RTOG 9410). The 4-year survival with concurrent cisplatin/vinblastine and once-daily irradiation was 21% vs 12% with sequential treatment ($P = .04$). The third treatment arm (concurrent cisplatin/oral etoposide and hyperfractionated irradiation) was intermediate, with a 4-year survival of 17%.

The role of altered radiation therapy fractionation, though, deserves further study. ECOG 2597 randomized patients after induction chemotherapy (with carboplatin and paclitaxel) to receive either standard radiation therapy (64 Gy/2 Gy fraction) vs hyperfractionated accelerated radiation therapy (HART), 57.6 Gy delivered 1.5 Gy tid over 2.5 weeks. Although the study closed prematurely

due to poor accrual (only 111 patients were eligible), the median survival in the investigational arm appeared promising (22 months).

Movsas et al reported the results of a quality-adjusted time without symptoms of toxicity (QTWiST) analysis of RTOG 94-10. Despite the increase in reversible nonhematologic toxicities in the concurrent arms, the overall mean toxicity was highest in the sequential arm, which involved the longest treatment time. The concurrent once-daily arm had the optimal QTWiST, further supporting concurrent chemoradiation therapy as a new treatment paradigm.

Recently, two randomized phase II trials also appear to support the use of concurrent chemoradiation therapy for locally advanced NSCLC. Choy et al performed a randomized phase II study in 276 patients of three chemoradiation therapy regimens with paclitaxel, carboplatin, and thoracic irradiation in their locally advanced multimodality protocol (LAMP). They found that concurrent chemoradiation therapy followed by adjuvant chemotherapy appeared to have the best therapeutic outcome, with a median survival of 16.1 months, compared with either induction chemotherapy followed by concurrent chemoradiation therapy (median survival, 11 months) or sequential chemotherapy followed by irradiation (median survival, 12 months).

Similarly, in another randomized phase II study, Zatloukal et al studied 102 patients treated with concurrent chemoradiation therapy and sequential chemotherapy followed by irradiation. The chemotherapy consisted of four cycles of cisplatin and vinorelbine (Navelbine). The investigators reported a median survival in the concurrent arm of ~20 months, vs ~13 months in the other arm ($P = .02$).

Movsas et al reported the results of the first Patterns of Care Study (PCS) for lung cancer, which was conducted to determine the national patterns of radiation therapy practice in patients treated for nonmetastatic lung cancer. As supported by clinical trials, the PCS for lung cancer demonstrated that patients with clinical stage III NSCLC received chemotherapy plus radiation therapy more than radiation therapy alone ($P < .0001$). In clinical stage I NSCLC, though, radiation therapy alone was the primary treatment ($P < .0001$). Factors correlating with increased use of chemotherapy included lower age ($P < .0001$), histology (SCLC > NSCLC, $P < .0001$), increasing clinical stage ($P < .0001$), increasing Karnofsky performance status ($P < .0001$), and lack of comorbidities ($P = .0002$) but not academic vs nonacademic facilities ($P = .81$). Of all patients receiving chemotherapy, approximately three-quarters received it concurrently with radiation therapy. Only 3% of all patients were treated on Institutional Review Board-approved trials, demonstrating the need for improved accrual to clinical trials.

New chemotherapeutic agents plus irradiation Several recent phase I/II trials evaluated carboplatin and paclitaxel given concurrently with thoracic irradiation. These studies showed acceptable toxicity and relatively high response rates, and in one of the studies, the 3-year survival rate was quite high (39%).

In addition to paclitaxel and carboplatin, many other chemotherapeutic agents with activity in NSCLC have emerged, including docetaxel (Taxotere),

vinorelbine, gemcitabine, UFT, and irinotecan (CPT-11, Camptosar). A trial from Japan tested induction chemotherapy with irinotecan and cisplatin followed by radiation therapy with weekly irinotecan (30 mg/m^2 during radiation therapy). The study reported a response rate of 65% and a median survival rate of 16.5 months, with a grade 3/4 esophagitis rate of only 4%.

Typically, it can be difficult to deliver systemic doses of chemotherapy following concurrent chemoradiotherapy. However, the Southwest Oncology Group (SWOG) recently reported a phase II study of concurrent chemoradiation therapy (cisplatin/etoposide) followed by consolidation docetaxel (75-100 mg/m^2 q21d × 3). This group of patients with pathologically documented stage IIIB NSCLC (pleural effusion excluded) had a promising median survival of 27 months. Toxicity during consolidation consisted primarily of neutropenia (56% grade 4).

Current treatment recommendations

At present, it is reasonable to consider concurrent chemoradiation therapy (with once-daily radiation therapy) as a new treatment paradigm in stage III (inoperable) lung cancer patients with an ECOG performance status of 0/1 who have not lost more than 5% of their usual body weight.

TREATMENT OF PATIENTS WITH STAGE IV DISEASE

Until recently, there was considerable controversy over the value of treating stage IV NSCLC patients with chemotherapy. Treatment with older cisplatin-containing regimens, such as cisplatin/etoposide, showed only a modest effect on survival, improving median survival by approximately 6 weeks, according to a meta-analysis, and yielding a 1-year survival rate of approximately 20% (as compared with a rate of approximately 10% for supportive care).

However, several newer chemotherapeutic agents have produced response rates in excess of 20% in NSCLC (Table 4). The potentially useful new agents include the taxanes (paclitaxel and docetaxel), vinorelbine, gemcitabine, and irinotecan. Several of these new drugs have unique mechanisms of action. Paclitaxel and docetaxel increase polymerization of tubulin; gemcitabine is an antimetabolite; and irinotecan is a topoisomerase I inhibitor.

Furthermore, randomized trials demonstrated that a combination of a newer agent plus cisplatin significantly improves the response rate over cisplatin monotherapy (historically considered the most active agent for NSCLC). This increase in response rate translates into significant, although modest, improvement in survival (Table 5).

Optimal chemotherapy for advanced NSCLC

Until the early 1990s, regimens of cisplatin plus a vinca alkaloid or etoposide were most common. More recently, regimens that employ newer agents are more widely used. However, choosing one regimen from many options is a difficult task because there is no survival advantage documented for one regimen over another or standard regimen vs regimens containing newer agents.

Table 6 summarizes the results of selected randomized trials in which combination regimens containing a newer agent are compared with old "standard" regimens or regimens containing another newer agent. Subtle differences in the eligibility criteria (eg, inclusion of patients with stage III tumors or those with poor performance status) make it difficult to directly compare the trial results. Nevertheless, there is a trend indicating that regimens containing newer agents show higher response rates and also better survival outcome in some series than do older regimens.

Movsas et al reported the results of RTOG 98-01, a phase III study of amifostine (500 mg IV 4×/wk) in patients with locally advanced NSCLC receiving chemotherapy and hyperfractionated radiation therapy. Seventy-three percent received amifostine per protocol or with minor deviation. On the amifostine arm, there were significantly higher rates of low-grade acute nausea and vomiting, acute cardiovascular toxicity, mostly transient hypotension, and episodes of acute infection/febrile neutropenia. The rate of grade ≥ 3 esophagitis was 30% with amifostine vs 34% without amifostine (P = .9). Based on daily patient diaries, though, the swallowing dysfunction area under the curve was lower with amifostine (P = .03). Overall, amifostine did not reduce grade ≥ 3 esophagitis per the NCI-CTC criteria. However, direct patient assessment suggests a possible advantage to amifostine that is being explored with modified dosing/route strategies *(Movsas B, Scott C, Langer C, et al: Proc Am Soc Clin Oncol [abstract] 22:636, 2003).*

Vinorelbine plus cisplatin combination

Vinorelbine was the first agent that demonstrated improved activity against NSCLC in combination with cisplatin. The European multicenter trial reported by LeChevalier showed the results favoring cisplatin plus vinorelbine combination (vinorelbine, 30 mg/m^2 weekly; cisplatin, 120 mg/m^2 on days 1 and 29, then every 6 weeks) over a vindesine plus cisplatin combination (vindesine, 3 mg/ m^2 weekly; cisplatin, 120 mg/m^2 on days 1 and 29, then every 6 weeks) and vinorelbine alone (30 mg/m^2 weekly). The median survival duration of 40 weeks in the vinorelbine/cisplatin treatment arm was significantly longer than the 32 weeks in the vindesine/cisplatin arm (P = .04) and 31 weeks in the vinorelbine monotherapy arm (P < .001). This trial, however, did not confirm the role of vinorelbine in NSCLC therapy, even though it confirmed the role of cisplatin.

To address this issue, SWOG conducted a study comparing cisplatin alone (100 mg/m^2 every 4 weeks) with vinorelbine/cisplatin combination (cisplatin, 100 mg/m^2 every 4 weeks; vinorelbine, 25 mg/m^2 weekly × 3 every 4 weeks). Survival outcome was analyzed for 415 patients, 92% with stage IV tumors. The vinorelbine/cisplatin treatment significantly improved the disease progression-free survival (median, 2 vs 4 months; P = .0001) and overall survival (median, 6 vs 8 months; 1-year survival 20% vs 36%; P= .0018).

Recently, Comella et al reported interim analysis results of a phase III trial of the Southern Italy Cooperative Oncology Group. A three-drug regimen (cisplatin, gemcitabine, and vinorelbine) was associated with a substantial survival gain over the cisplatin and vinorelbine regimen (median survival time, 51 and 35 weeks, respectively).

TABLE 4: Active newer agents for NSCLC chemotherapy

Agent	Number of studies	Number of patients	Response rate (%) (range)
Irinotecan	3	150	34 (32-37)
Docetaxel	7	257	33 (21-54)
Paclitaxel	4	151	22 (10-24)
Gemcitabine	7	566	21 (20-26)
Vinorelbine	4	501	21 (12-32)

Paclitaxel plus platinum compound A number of studies demonstrate promising results with paclitaxel in combination with cisplatin or carboplatin and other agents. Two large randomized trials compared paclitaxel plus cisplatin with standard regimens. In a three-arm, randomized ECOG trial (ECOG 5592) reported by Bonomi et al, 600 eligible patients with chemotherapy-naive stage IIIB to IV NSCLC were randomly assigned to receive a combination of cisplatin (75 mg/m^2) plus etoposide (100 mg/m^2 daily on days 1 to 3) vs either low-dose (135 mg/m^2 over 24 hours) or high-dose (250 mg/m^2 over 24 hours with growth factor) paclitaxel plus cisplatin (75 mg/m^2). The response rates for the low-dose and high-dose paclitaxel arms were 26.5% and 32.1%, respectively, significantly better than the cisplatin/ etoposide arm (12.0%). Superior survival was observed with the combined paclitaxel regimens (median survival time, 9.99 months; 1-year survival rate, 39.1%) compared with etoposide plus cisplatin (median survival time, 7.69 months; 1-year survival rate, 31.6%; $P = .048$). Comparing survival rates for the two dose levels of paclitaxel revealed no significant differences.

In a European trial of similar design reported by Giaccone et al, cisplatin/ paclitaxel improved the response rate and quality-of-life parameters. There was no improvement in overall survival, however, compared with a standard regimen of cisplatin/teniposide (Vumon).

Paclitaxel/carboplatin has been the most widely favored regimen for first-line chemotherapy in all NSCLC stages among US medical oncologists, mainly due to promising phase II trial results and the ease of administration as outpatients, with manageable toxicity profiles compared with cisplatin-containing regimens. One of the early phase II trials, for example, reported a response rate of 62%, a median survival duration of 53 weeks, and a 1-year survival rate of 54%. However, a randomized trial sponsored by the manufacturer of paclitaxel failed to demonstrate a survival advantage over the standard cisplatin plus etoposide regimen. Nevertheless, paclitaxel plus carboplatin may remain a community standard because a recently completed SWOG trial reported results equivalent to the time-tested vinorelbine/cisplatin regimen (see Table 6).

Second-line chemotherapy A randomized phase III study conducted by the CALGB further supported the superiority of combination chemotherapy over

TABLE 5: Results of selected randomized trials of chemotherapy comparing cisplatin alone vs cisplatin plus a newer agent in advanced NSCLC

Investigator	Chemotherapy regimen	Pts (n)	Response rate (%)	Median survival (mo)	1-yr survival (%)
Klastersky (1989)	Cisplatin	81	19	6.0	NA
	Cisplatin + etoposide	81	26[a]	5.	NA
Wozniak (1998)	Cisplatin	209	12	6	20
	Cisplatin + vinorelbine	206	26	8[a]	36[a]
Gatzemeier (1998)	Cisplatin	206	17	8.6	NA
	Cisplatin + paclitaxel	202	26[a]	8.1	NA
Sandler (1998)	Cisplatin	262	10	7.6	28
	Cisplatin + gemcitabine	260	26[a]	9.0[a]	39[a]
Von Pawel (1998)	Cisplatin	219	13.7	6.3	21
	Cisplatin + tirapazamine	218	27.5[a]	8.5[a]	33[a]

[a] The difference between the groups was statistically significant ($P < .05$).

NA = data not available

single-agent therapy. Previous trials had indicated that a platinum plus a novel agent was superior to a platinum alone. Lilenbaum et al demonstrated that for patients with stage IIIB-IV NSCLC, carboplatin and paclitaxel are superior to paclitaxel alone, even for patients with a performance status of 2. This randomized trial showed a median survival advantage for the combination therapy.

Gemcitabine plus cisplatin Gemcitabine is also approved by the FDA for use against NSCLC based on a series of successful phase II trials of cisplatin/gemcitabine and three major phase III trials. The Hoosier Oncology Group study, reported by Sandler et al, compared gemcitabine/cisplatin with cisplatin alone and showed a modest improvement in median and 1-year survival comparable to that seen in the vinorelbine trials (Table 5). The Spanish and Italian trials, reported by Cardenal et al and Crino et al, compared gemcitabine plus cisplatin with standard-regimen cisplatin plus etoposide and mitomycin plus ifosfamide plus cisplatin, respectively. Although there was a significant improvement in overall response, these two studies failed to demonstrate a survival benefit.

Since gemcitabine is relatively well tolerated without dose-limiting myelosuppression, it is being evaluated for use as a single agent or in combination with other agents in older or medically compromised patients. Italian investigators report that gemcitabine combined with vinorelbine regimen is associated with significantly better survival than single-agent vinorelbine in elderly patients with NSCLC.

Other combination regimens that contain cisplatin plus newer agents, such as docetaxel or irinotecan, also showed similar results when compared with other two-drug regimens of either two newer or two older agents (Table 6).

Major randomized trials comparing new regimens

To identify a better chemotherapy regimen for advanced-stage NSCLC, the US cooperative study groups conducted large phase III trials. The SWOG investigators compared paclitaxel/carboplatin with vinorelbine/cisplatin (the time-tested regimen in previous European and SWOG trials). A total of 404 evaluable patients were randomized to receive either paclitaxel (225 mg/m^2 over 3 hours) plus carboplatin (at an area under the curve [AUC] of 6 mg/mL × min on day 1) every 21 days or vinorelbine (25 mg/m^2 weekly) plus cisplatin (100 mg/m^2 on day 1) every 28 days. Overall response rates were 27% for both groups. The median survival times were also identical (8 months), with virtually identical 1-year survival rates (35% and 33%, respectively). Although both regimens provided effective palliation for advanced NSCLC, the investigators identified paclitaxel/carboplatin for future studies because of a favorable toxicity profile and better tolerability and compliance.

The ECOG 1594 trial compared three platinum-based regimens containing new agents in the treatment of NSCLC with a control arm of cisplatin and paclitaxel. The regimens were gemcitabine (1,000 mg/m^2 on days 1, 8, and 15) plus cisplatin (100 mg/m^2 on day 1) every 4 weeks, docetaxel (75 mg/m^2) plus cisplatin (75 mg/m^2 on day 1) every 3 weeks, and paclitaxel (225 mg/m^2 over 3 hours) plus carboplatin (at AUC of 6 mg/mL × min on day 1) every 21 days; the reference regimen was paclitaxel (175 mg/m^2 over 24 hours) plus cisplatin (75 mg/m^2 on day 1) every 21 days.

Analysis of 1,163 eligible patients showed no statistically significant differences in overall response rates, median survival, and 1-year survival rates when compared with the control arm, paclitaxel and cisplatin. Gemcitabine plus cisplatin was associated with a statistically significant prolongation of time to disease progression when compared with the control arm (4.5 vs 3.5 months, $P = .002$) but was also associated with a higher percentage of grade 4 thrombocytopenia, anemia, and renal toxicity.

Since all the regimens showed similar efficacy, quality of life becomes a critical issue in choosing a particular regimen. The decision to use one regimen over another will depend not only on ease of administration and side effects, but also on the personal preference and experience of the treating oncologist.

Second-line chemotherapy for NSCLC

Before the new generation of more effective agents became available, few, if any, significant benefits were expected from second-line chemotherapy. As a result, reports in the literature seldom address this issue specifically or systematically. The most experience with second-line chemotherapy in NSCLC is with docetaxel, which has received FDA approval for this indication based on two randomized phase III trials confirming the promising phase II results of docetaxel monotherapy in patients with advanced NSCLC previously treated with platinum-based chemotherapy.

TABLE 6: Results of selected randomized trials evaluating chemotherapy regimens of newer agents in advanced NSCLC

Investigator	Chemotherapy regimen	No. of patients	Response rate (%)	Median survival	1-yr survival rate (%)
LeChevalier (1994)	Vinorelbine + cisplatin	206	30	40 wk	35
	Vindesine + cisplatin	200	19	32 wk	27
	Vinorelbine	206	14	31 wk	30
Bonomi (1996)	Etoposide + cisplatin	600 (total)	12.0	7.69 mo	31.6
	Paclitaxel + cisplatin		26.5	9.56 mo	36.9
	Paclitaxel + cisplatin + G-CSF		32.1	9.99 mo	39.1
Giaccone (1997)	Teniposide + cisplatin	157	28	9.9 mo	41
	Paclitaxel + cisplatin	152	41	9.7 mo	43
Belani (1998)	Etoposide + cisplatin	179	14.0	9.9 mo	37
	Paclitaxel + carboplatin	190	21.6	9.5 mo	32
Crino (1998)	Mitomycin + ifosfamide + cisplatin	152	28	38 wk	NA
	Gemcitabine + cisplatin	154	40	35 wk	NA
Georgoulias (1999)	Docetaxel + cisplatin	152	32	10 mo	42
	Docetaxel + gemcitabine	144	34	9 mo	34
Masuda (1999)	Irinotecan + cisplatin	378 (total)	43	50.3 wk	47.5
	Vindesine + cisplatin		31	47.4 wk	37.9
	Irinotecan		21	46.1 wk	40.7
Kelly (1999)	Paclitaxel + carboplatin	184	27	8 mo	36
	Vinorelbine + cisplatin	181	27	8 mo	33
Schiller (2000)	Paclitaxel + cisplatin	1,163 (total)	21.3	7.8 mo	31
	Gemcitabine + cisplatin		21.0	8.1 mo	36
	Docetaxel + cisplatin		17.3	7.4 mo	31
	Paclitaxel + carboplatin		15.3	8.2 mo	35
Frasci (2000)	Gemcitabine + vinorelbine	60	22	29 wk	30
	Vinorelbine	60	15	18 wk	13
Lilenbaum (2002)	Paclitaxel + carboplatin	292	29	10 mo	NA
	Paclitaxel	290	17	8.6 mo	NA

G-CSF = granulocyte colony-stimulating factor; NA = data not available

In a multicenter US trial reported by Fossella et al, 373 patients were randomized to receive either docetaxel, 100 mg/m^2 (D100) or 75 mg/m^2 (D75) vs a control regimen of vinorelbine (30 mg/m^2/wk) or ifosfamide (2 g/m^2 × 3 days) every 3 weeks. Overall response rates were 10.8% with D100 and 6.7% with D75, each significantly higher than the 0.8% response of the control arm (P= .001 and P= .036, respectively). Although overall survival was not significantly different among the three groups, the 1-year survival was significantly higher with D75 than with the control treatment (32% vs 19%; P= .025).

The second trial reported by Shepherd et al compared single-agent docetaxel with best supportive care. The initial docetaxel dose was 100 mg/m^2, which was changed to 75 mg/m^2 midway into the trial because of toxicity. A total of 204 patients were enrolled; 49 received D100, 55 received D75, and 100 received best supportive care. Treatment with docetaxel was associated with significant prolongation of survival (7.0 vs 4.6 months; log-rank test, $P = .047$) and time to disease progression (10.6 vs 6.7 weeks, $P < .001$).

Duration of chemotherapy

The American Society of Clinical Oncology (ASCO) has recommended that no more than eight cycles of chemotherapy be administered to patients with stage IV NSCLC. However, therapy should be individualized depending on the quality of tumor response and the patient's tolerance.

Novel and promising agents

Several novel agents are being developed for the treatment of solid tumors, including lung cancer. For example, farnesyl transferase inhibitors target prenylation of the *ras* family of proto-oncogenes. Farnesylation causes the *ras* oncogene to be constitutively active.

Other novel agents include signal transduction inhibitors, such as tyrosine kinase inhibitors (eg, erlotinib [Tarceva], gefitinib [Iressa]), antiangiogenic agents, and monoclonal antibodies (C225 [antiepidermal growth factor receptor antibody] and trastuzumab [Herceptin]). Many of these novel agents are being tested in combination with chemotherapeutic agents, as their mechanisms of action suggest that they may be far more effective as chronic inhibitors of cancer progression than as classic cytotoxics.

To date, most phase I studies of these various compounds have suffered from a difficulty in developing pharmacologically or molecularly driven end points that will serve as reasonable intermediate biomarkers of efficacy or even surrogates for toxicity. Further research has focused on the novel small molecule tyrosine kinase inhibitors erlotinib and gefitinib. Two phase II trials of gefitinib in the second- and third-line settings were conducted in Europe and Japan. Patients were randomized to receive either 250 mg/d or 500 mg/d. The drug was found to be active, with an 11%-18% response rate, and there was no superiority for the higher dose. Similar data were seen for erlotinib.

Unfortunately, randomized combination trials of gefitinib at 250 and 500 mg/d with cytotoxic chemotherapy, either paclitaxel and carboplatin in one trial or gemcitabine and cisplatin in the other study vs placebo in front-line therapy, failed to demonstrate any survival advantage. These results have cast a pall over the development of tyrosine kinase inhibitors in combination with chemotherapy. Regardless, the question of whether or not to approve these new agents for third-line therapy of lung cancer in cisplatin/docetaxel-refractory patients remains open for debate.

The activity demonstrated by the tyrosine kinase inhibitors gefitinib and erlotinib as single agents in advanced NSCLC generated much optimism, including a

recent trial indicating that erlotinib improved survival (by a median of 2 months) in the second- and third-line treatment of NSCLC, with a substantial increase in 1-year survival ($P < .001$). After the initial successes with chemotherapy and promising results from targeted tyrosine kinase inhibitors in stages IIIB and IV NSCLC, several large phase III trials of either gefitinib or erlotinib in combination with conventional platinum-based chemotherapy were conducted as the INTACT 1 and INTACT 2 trials or the TALENT and TRIBUTE trials.

Unfortunately, these large trials indicated no benefit to adding the tyrosine kinase inhibitors to conventional chemotherapy. A phase III trial combining the farnesyl transferase inhibitor lonafarnib (Sarasar) with paclitaxel and carboplatin in unselected, untreated patients with stage IIIB/IV NSCLC also failed to yield a survival advantage, despite promising phase I and II data. There was evidence that the combination of the chemotherapy with the signal transduction inhibitors was potentially detrimental. The placebo plus chemotherapy results initially showed a survival benefit over the first 6 months in two of these four trials. Survival data after 6 months from the INTACT II and the TRIBUTE trial indicate that from that point forward, patients who remained on erlotinib or gefitinib appeared to have a significant survival benefit, when compared with placebo.

In general, there appears to be little to favor triplet cytotoxic drug combinations vs doublet combinations in NSCLC. An area of great excitement, however, has been the addition of novel biologically or molecularly targeted agents to cytotoxic chemotherapy combinations. Several recent trials have demonstrated the potential advantages of adding a small molecule targeted to either the epidermal growth factor receptor (EGFR) or *ras* (namely the farnesyl transferase inhibitors). The interest in these agents in advanced NSCLC appears to have superseded the new cytotoxic agents with activity in other diseases, such as oxaliplatin (Eloxatin), tirapazamine, and UFT. A phase III combination of farnesyl transferase with paclitaxel and carboplatin failed to show superiority over paclitaxel and carboplatin.

The mechanisms of action of these new small molecules are widely divergent, and their combinations with the cytotoxics may not necessarily lead to an enhanced response rate. Khuri and colleagues demonstrated, however, that the combination of cisplatin, vinorelbine, and bexarotene (Targretin, a retinoid-X-receptor [RXR]-specific novel retinoid) resulted in substantial median and 2-year survival rates in patients with stage IIIB NSCLC with malignant pleural effusion or stage IV NSCLC. Median survival in this multicenter study was 14 months in the phase II portion; 2-year survival was 32%; and 3-year survival was 18%. The combination yielded modest response rates (25%), not markedly superior to what was expected with cisplatin and vinorelbine alone.

This finding has led to an uncoupling of the requirement for higher response rates when adding cytotoxic agents to one another in the belief that adding these novel biologic agents may lead to enhanced survival. There now appears to be a great deal of promise associated with several small molecules, either alone or combined with chemotherapy. Novel agents such as gefitinib or the farnesyl transferase inhibitor lonafarnib have shown promising efficacy in small

A phase III trial of 731 patients conducted by the National Cancer Institute of Canada Clinical Trials Group sought to determine whether erlotinib (Tarceva) prolonged survival in patients with advanced NSCLC whose disease had progressed after first- or second-line chemotherapy. The overall response rate to erlotinib was 8.9% ($P < .001$), with a median response duration of 34.3 weeks. Overall survival (6.7 vs 4.7 mo, $P = .001$) and disease progression-free survival (2.23 vs 1.84 mo, $P < .001$) were significantly greater in the erlotinib arm than in the placebo arm. (*Shepherd FA, et al: Proc Am Soc Clin Oncol [late-breaking abstract 7022] 23, 2004*). Tarceva was approved for second-line treatment of advanced NSCLC in November 2004.

trials that have included patients with NSCLC; gefitinib alone resulted in an 18% response rate in second- or third-line therapy for NSCLC in a study population recruited across several continents.

Some provocative phase I and II data with both bexarotene and lonafarnib in combination with chemotherapy have led to the recent launch of phase III trials of both agents in combination with cytotoxic chemotherapy. These trials are ongoing and are expected to accrue between 600 and 800 patients over the next 2 years. The trials will test whether the preclinical and clinical synergy seen with these compounds and either platinums or taxanes is vindicated in phase III front-line trials of NSCLC.

Current treatment recommendations It is important to note that patients who have lost significant amounts of weight or who have poor performance status are at greater risk for toxicity, including a higher likelihood of lethal toxicity, when they are treated with modest doses of chemotherapy. Based on currently available data, a reasonable approach for patients with stage IV NSCLC who have good performance status (ECOG performance status 0/1) and have not lost a significant amount of weight (< 5% of usual weight) would be to encourage them to participate in a clinical trial.

However, it would also be appropriate to treat this group of patients with etoposide plus cisplatin or with one of the newer combination regimens, such as gemcitabine/cisplatin, vinorelbine/cisplatin, paclitaxel/cisplatin, paclitaxel/carboplatin, or docetaxel/cisplatin (Tables 7 and 8).

ROLE OF PHOTODYNAMIC THERAPY

Photodynamic therapy (PDT), which combines Photofrin (a hematoporphyrin derivative in which the less active porphyrin monomers have been removed) with an argon-pumped dye laser, has been explored in a variety of different tumors, with varying results. Several investigators have reported excellent results with PDT in early-stage head and neck cancers, as well as intrathoracic tumors. However, initial studies have involved a limited number of patients.

Although this novel technique seems to be extremely promising, it appears to be applicable to only a small minority of patients with NSCLC. Nevertheless, PDT appears to be particularly useful for the treatment of early-stage lung cancer for a variety of reasons. First, it appears to preserve lung function and can be repeated as additional tumors appear–an important consideration since such patients appear to be at high risk for developing other new tumors. Second, this

technique does not preclude ultimate surgical intervention when deemed necessary.

Results in early-stage NSCLC Perhaps most striking are the results reported by Furuse et al, who treated 54 patients with 64 early-stage lung cancers using Photofrin (2.0 mg/kg) and 630-nm illumination of 100-200 J/cm^2. Of 59 accessible tumors, 50 responded completely and 6 showed partial responses. Five of the complete responders developed recurrences 6-18 months after treatment.

The major predictor of response in this study was tumor length. The likelihood of achieving a complete response was 97.8% if the tumor was < 1 cm, as opposed to only 42.9% if the lesion was > 1 cm. The overall survival rate in these patients was 50% at 3 years.

In a phase III trial led by Hanna et al, 572 previously treated patients were randomized to receive pemetrexed (Alimta) with vitamin B_{12}, folic acid, and dexamethasone or docetaxel (Taxotere) with dexamethasone. The overall response rate in the pemetrexed arm was higher, 9.1% vs 8.8%. The median disease progression-free survival was 2.9 months for each arm, and the median survival favored pemetrexed (8.3 vs 7.9 mo). The 1-year survival for each arm was 29.7%. Adverse reactions (grade 3/4) were more severe with docetaxel (*Hanna N, Shepherd FA, Fossella FV, et al: J Clin Oncol 22:1589-1597, 2004*).

A similar study by Kato et al also indicated a 96.8% complete response rate for tumors < 0.5 cm but only a 37.5% rate for tumors > 2 cm. The overall 5-year survival rate for the 75 patients treated in this study was 68.4%, which is acceptable by current standards.

Further work by Lam et al supported these promising results of PDT in early-stage NSCLC.

Results in advanced-stage NSCLC Two prospective, randomized trials (European; US/Canadian) compared PDT with the neodymium:yttrium-aluminum-garnet (Nd:YAG) laser for partially obstructive, advanced NSCLC. Investigators analyzed results from the two trials both individually and collectively. Collective analysis included data from 15 centers in Europe and 20 centers in the United States and Canada and involved a total of 211 patients. In the European trial, 40% of the patients had received prior therapy, whereas in the US/Canadian trial, all of the patients had received previous treatment.

Tumor response was similar for both therapies at 1 week. However, at 1 month, 61% and 42% of the patients treated with PDT in the European and US/Canadian trials, respectively, were still responding, compared with 36% and 19% of patients who underwent laser therapy in the two trials.

PDT also produced more dramatic improvements in dyspnea and cough than did Nd:YAG therapy in the European trial, but the two treatments had similar effects on these symptoms in the US/Canadian trial. Both sets of investigators concluded that PDT appears to be superior to laser therapy for the relief of dyspnea, cough, and hemoptysis. Also, the overall incidence of adverse reactions was similar with the two therapies (73% for PDT vs 64% for Nd:YAG therapy). Early-stage lung cancer, most specifically endobronchial squamous cell carcinomas smaller than 1 cm, is effectively treated, with a complete response rate of 75% and a recurrence rate of 30% over 5 years.

TABLE 7: Single-agent chemotherapy regimens for NSCLC

Drug	Dose and schedule
Vinorelbine	30 mg/m^2 IV weekly
LeChevalier T, Brisgand D, Douillard J-Y, et al: J Clin Oncol 12:360–367, 1994.	
Vinorelbine	For patients 70 years old or older: 30 mg/m^2 IV on days 1 and 8, every 21 days
Gridelli C, Perrone F, Cigolari S, et al: Proc Am Soc Clin Oncol [abstract] 20:308a, 2001.	
Docetaxel	75 mg/m^2 IV on day 1 every 3 weeks
Shepherd FA, Dancey J, Ramlau R, et al: J Clin Oncol 18:2095–2103, 2000.	
Pemetrexed	500 mg/m^2 IVPB every 3 weeks
Dexamethasone (4 mg by mouth twice daily) should be started a day before and a day after pemetrexed. All patients should also receive folic acid (350-1,000 mg/d) started about a week before and thereafter while taking pemetrexed. Vitamin B_{12} (1,000 mg IM) should be started about 1 to 2 weeks before pemetrexed and every 9 weeks while taking pemetrexed.	
Hanna N, Shepherd F, Fossella FV, et al: J Clin Oncol [abstract] 22:1589–1597, 2004.	
Gefitinib	250 mg orally once a day
Kris MG, Natale RB, Herbst RS, et al: JAMA 290:2149–2158, 2003.	
Gemcitabine	1,000 mg/m^2 IV on days 1, 8, and 15 every 4 weeks
Vansteenkiste J, Vandebroek J, Nackaerts K, et al: Proc Am Soc Clin Oncol [abstract] 19:1910a, 2000.	

Table prepared by Ishmael Jaiyesimi, DO

PALLIATION OF LOCAL AND DISTANT SYMPTOMS

Radiation therapy

Many patients with lung cancer experience distressing local symptoms at some time. They may arise from airway obstruction by the primary tumor, compression of mediastinal structures by nodal metastases, or metastatic involvement of distant organs. Radiation therapy is effective in palliating most local symptoms, as well as symptoms at common metastatic sites, such as bone and brain. For selected patients with a solitary brain metastasis and controlled disease in other sites, resection followed by irradiation appears to be superior to radiation therapy alone in improving both survival and quality of life.

Recent studies have demonstrated varying degrees of benefit for strategies beyond palliative whole-brain radiation therapy (WBRT) in the management of brain metastases. Sperduto et al reported the results of RTOG 95-08, a randomized trial comparing WBRT (3,750 cGy in 250 cGy fractions) vs WBRT

and stereotactic radiosurgery (SRS) in 333 patients with one to three brain metastases. They found a statistically significant survival advantage with WBRT and SRS for the stratified group of patients with solitary brain metastases (mean survival, 6.5 vs 4.9 months; $P = .04$). Other subsets that appeared to benefit included those with NSCLC. Patients in the WBRT and SRS group were more likely to have a stable or improved performance status than those in the WBRT-alone group.

In another randomized trial, 401 patients with unresected brain metastases (Karnofsky performance score > 70) were randomized to receive WBRT (30 Gy) with or without the redox mediator motexafin gadolinium (MGd). Overall, there was no improvement in survival, but time to neurologic disease progression (as determined by investigators) was significantly prolonged with MGd ($P = .02$). Interestingly, the benefit of MGd was primarily seen in lung cancer (which made up 63% of the cases). This has led to a trial of this agent specifically for patients with brain metastases from NSCLC.

A large prospective trial of gefitinib (Iressa) in patients with bronchoalveolar carcinoma (BAC) conducted by the Southwest Oncology Group (SWOG S0126), found that 19% of 102 previously untreated patients with measurable disease responded to the drug. Among 67 chemotherapy-naive patients with measurable disease, the response rate was 21%. In 21 previously treated patients, the response rate was 10%. The median survival was 12 months and 10 months for chemotherapy-naive and previously treated patients, respectively. The 1-year survival in each group was about 50%. Adverse events included acneiform rash and diarrhea (*West H, Franklin WA, Gumerlock PH, et al: Proc Am Soc Clin Oncol [abstract] 23:618, 2004*).

In another randomized trial, Antonadou et al compared WBRT with or without temozolomide (TMZ, Temodar), 75 mg/m^2 daily during WBRT and 1 month afterward (at 200 mg/m^2) on days 1-5 q 28 days × six cycles. A total of 134 eligible patients were randomized to undergo treatment, 82% with lung primaries. Median survival was 8.3 months in the TMZ plus WBRT arm and 6.3 months in the WBRT arm ($P = .18$). Of note, a significantly higher response rate was observed in the combined-modality arm (53%) than in the WBRT arm (33%, $P = .04$). The optimal management of patients with brain metastases should be tailored to the individual situation.

Doses In the United States, radiation oncologists often use doses of ~30 Gy in 10 fractions for palliative treatment in lung cancer. Data from the United Kingdom suggest that similar efficacy without greater toxicity may be achieved with more abbreviated schedules, such as 17 Gy in 2 fractions 1 week apart or single fractions of 10 Gy (see Table 9). Such schedules may facilitate the coordination of irradiation and chemotherapy and also reduce patient travel and hospitalization.

Recently, just over 400 patients with inoperable NSCLC (stage III/IV) were randomized to receive three different fractionation regimens (8.5 Gy × 2, 2.8 Gy × 15, or 2.0 Gy × 25). Using the EORTC Quality-of-Life Questionnaire (QLQ) C-30 with the lung cancer-specific module (LC-13), Sundstrom et al found the effect of hypofractionated irradiation (17 Gy in 2 fractions) was comparable to that with longer fractionation schemes with regard to symptom relief and survival.

TABLE 8: Combination chemotherapy regimens recommended for NSCLC

Regimen	Agents	Dose and schedule	Treatment interval
PE	Platinol Etoposide	60 mg/m^2 IV on day 1 120 mg/m^2 IV on days 1-3	3 weeks
MIC	Mitomycin Ifosfamide Cisplatin	6 mg/m^2 IV on day 1 3 g/m^2 IV on day 1 100 mg/m^2 IV on day 2	4 weeks
PT	Platinol Taxol	75 mg/m^2 IV on day 2 135 mg/m^2 IV on day 1 (24-h infusion)	3 weeks
CP	Carboplatin Paclitaxel	AUC of 6 IV on day 1 225 mg/m^2 IV on day 1 (3-h infusion)	3 weeks
PG	Platinol Gemcitabine	100 mg/m^2 IV on day 1 1,000 mg/m^2 IV on days 1, 8, and 15	4 weeks
PD	Platinol Docetaxel	75 mg/m^2 IV on day 1 75 mg/m^2 IV on day 1	3 weeks
PV	Platinol Vinorelbine	100 mg/m^2 IV on day 1 25 mg/m^2 IV on days 1, 8, 15, and 22	4 weeks
GV	Gemcitabine Vinorelbine	1,200 mg/m^2 IV on days 1 and 8 30 mg/m^2 IV on days 1 and 8	3 weeks

AUC = area under the curve

Endobronchial irradiation with cobalt-60 or iridium-192 has been used to palliate symptoms arising from partial airway obstruction, including cough, dyspnea, and hemoptysis. The dosimetric advantage of being able to deliver a high radiation dose to the obstructing endobronchial tumor while sparing adjacent normal structures, such as the lungs, spinal cord, and esophagus, has clear appeal, particularly in the patient whose disease has recurred following prior external-beam irradiation. Although good rates of palliation have been reported with endobronchial irradiation, significant complications, including fatal hemoptysis, are seen in 5%-10% of patients. It remains unclear, however, how often this complication is actually due to the irradiation vs the underlying disease itself.

Endobronchial irradiation should be considered as only one of several approaches (including laser excision, cryotherapy, and stent placement) that can be used in the management of patients with symptomatic airway obstruction, and management should be individualized. All of these approaches are more suitable for partial than for complete airway obstruction.

TABLE 9: Percentage of patients with symptoms of NSCLC palliated by external-beam irradiation

Symptom	Standard RT (24-30 Gy in 6-10 fractions)	17 Gy in 2 fractions (first trial/second trial)	1 fraction of 10 Gy
Cough	56	65/48	56
Hemoptysis	86	81/75	72
Chest pain	80	75/59	72
Anorexia	64	68/45	55
Depression	57	72/NA	NA
Anxiety	66	71/NA	NA
Breathlessness	57	66/41	43

NA = data not available; RT = radiation therapy

Data from Bleehen NM, Girling DJ, Fayers PM, et al: Br J Cancer 63:265–270, 1991; Bleehen NM, Bolger JJ, Hasleton PS, et al: Br J Cancer 65:934–941, 1992.

Chemotherapy

Several recent trials have explored the use of chemotherapy to palliate specific symptoms in patients with lung cancer. In general, these trials have found that rates of symptomatic improvement were considerably higher than objective response rates and were not dissimilar to symptomatic response rates with local radiation therapy.

A randomized phase II study suggests that rhuMAb vascular endothelial growth factor (VEGF; 15 mg/kg) in combination with carboplatin/paclitaxel chemotherapy may increase response rates and prolong time to disease progression in patients with previously untreated NSCLC when compared with carboplatin/paclitaxel chemotherapy alone. Patients with progressive disease who received carboplatin/paclitaxel alone were allowed to cross over to receive rhuMAb VEGF. The median survival time was 7.7 months with high-dose rhuMAb VEGF (15 mg/kg q3wk) and 4.9 months with carboplatin/paclitaxel alone. Although sudden and life-threatening hemoptysis occurred in six rhuMAb VEGF-treated subjects and was fatal in four, survival data are encouraging, and a phase III trial is in progress without crossover to rhuMAb VEGF.

Thus, although radiation therapy remains the most appropriate modality for the treatment of such problems as superior vena cava obstruction, spinal cord compression, brain metastases, or localized bone pain, patients who have more extensive disease without these local emergencies may be considered for palliative chemotherapy, which may relieve local symptoms and prolong survival.

Bisphosphonates

Approximately 30%-65% of patients with advanced lung cancer develop bone metastases. The median survival following development of bone metastases is 6 months. Bone disease is associated with significant morbidity, including severe pain, hypercalcemia of malignancy, pathologic fracture, and spinal cord or nerve root compression. Treatment of bone metastases may include surgical intervention, radiation therapy, and chemotherapy. Bisphosphonate treatment can decrease skeleton-related complications, delay progressive disease, and relieve bone pain.

Bisphosphonates such as clodronate, pamidronate (Aredia), and zoledronic acid (Zometa) exhibit strong affinity for the hydroxyapatite crystal of bone and preferentially accumulate at sites of active bone remodeling, where they prevent bone resorption. They provide effective treatment for hypercalcemia of malignancy and have been shown to delay the onset of progressive bone disease and relieve bone pain in studies largely performed in patients with metastases secondary to breast cancer, multiple myeloma, and prostate cancer. Nitrogen-containing bisphosphonates, such as pamidronate and zoledronic acid, appear to exert antitumor effects. Zoledronic acid has also been found to have pronounced antinociceptive effects, which have been absent with other bisphosphonates in preclinical studies. Zoledronic acid is the only bisphosphonate shown to be effective in reducing skeletal complications in patients with bone metastases from lung cancer and solid tumors other than breast and prostate cancers.

Follow-up of long-term survivors

At present, no standard follow-up protocol exists for patients with cured NSCLC or SCLC. However, at a minimum, long-term follow-up should include serial physical examinations once the patient has reached the 5-year mark. Controversy currently exists about the value of utilizing CT scanning or even chest x-rays for the long-term follow-up of these patients.

In this vein, retrospective reviews of the literature have revealed that patients with SCLC appear to have the highest rate of second primary tumor development–as high as 30%–over the course of their lifetime, with some studies reporting annual second primary tumor rates of 5%-10%. Therefore, the concept of chemoprevention appears to have particular merit in these patients.

A recently completed, randomized chemoprevention study of patients with stage I NSCLC showed a surprisingly high annual recurrence rate of 6.5% in patients with T1 tumors, as opposed to 11.2% in patients with T2 tumors. Whether retinoids are effective chemopreventive agents remains to be seen. Nevertheless, there is clearly a need for effective chemoprevention for both of these tumor subsets, as well as the establishment of consistent guidelines for routine long-term follow-up. Given the current controversy over lung cancer screening, however, it is unlikely that this issue will be resolved without the performance of another prospective screeing trial.

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